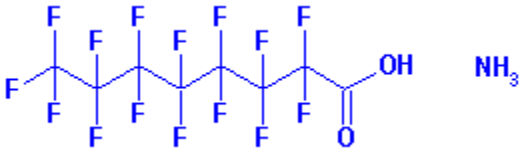

Michigan's Contaminant Induced Human Health Crisis

Addressing Michigan's Future
By
Facing the Challenge of the Evolving Nature of Environmental Contamination

Prepared for the Director of the Michigan Department of Environmental Quality

By
Robert Delaney
&
Dr. Richard DeGrandchamp

Introduction/Executive Summary
Michigan's Human Health Crisis
Addressing Michigan's Future
By
Facing the Challenges of the Evolving Nature of Environmental Contamination

By Robert Delaney

The State of Michigan and the United States (U.S) as a whole are in the midst of a human health crisis. The rates of various neurologic disorders (such as attention deficit hyperactivity disorder, autism, and schizophrenia), and autoimmune diseases (such as diabetes and multiple sclerosis) have been rapidly increasing across the nation. These diseases have tragic consequences for individuals and their families. These diseases place a great burden on the medical system, render the overall population less productive as individuals, and take primary care givers away from other productive pursuits. There is an ever increasing amount of evidence that these impacts to our health as a state and nation are the result of contaminants in our food, water, homes, air, and the general environment.

Currently, the U.S. Environmental Protection Agency has approximately 85,000 chemicals listed as in commercial use with 1,000 to 3,000 new chemicals coming in to use in the economy each year. Virtually nothing is known about the toxicity and environmental fate and transport of these chemicals. There are approximately 400 hazardous chemicals that have been detected in human umbilical cord blood, exposing the most chemically sensitive portions of our population to unknown risks. We are essentially running a large toxicity study and using the human population as the guinea pigs.

To explore this topic, this write up consists of five different issue papers. Three issue papers consist of an analysis of perfluoroalkyl chemicals (PFCs). The first paper consists of an overview of the nature and extent of PFC contamination in Michigan's environment. The second paper consists of a summation of the toxicological information that is available on PFCs. The second issue paper discusses the epidemiological studies on PFCs, and the evidence of health effects on human populations from PFCs.

The fourth paper provides a summation of the epidemiological evidence of dramatic increases in neurologic and autoimmune diseases observed in the U.S. human population. It also provides a couple of examples of ubiquitous contaminants that have been linked to population-wide, negative health effects.

The fifth and final paper consists of some recommendation on what the Michigan Department of Environmental Quality and Michigan State government should do in response to these rising epidemics. The fifth paper is essentially a "brain storming" exercise to point out that there are things that can be accomplished if we choose to do something to address our problems.

The reader is advised to start with the fourth white paper on the epidemiological evidence of the widespread increases in the rates of neurologic and autoimmune diseases in the general U.S. population (and abroad), if the reader is unfamiliar with the topic. That is the starting point for considering whether what we are doing is effective in protecting our citizens.

Finally, very little is said about the impact of contaminants on the biota in these issue papers. However, the chemicals negatively impacting humans are also damaging the environment.

These adverse environmental impacts should not be discounted. People with an understanding of the relationships between environmental quality, biological effects, and human impacts realize that the same contaminants that influence our health will also alter the environment. However, it is easier for most people to understand human health impacts that they can see all around them, than to understand more esoteric questions of reproductive rates of obscure biota, etc.

Particularly concise and essential references are provided to the readers to allow for rapid checking of facts, analysis, and data, etc. Additional references are noted in the bibliography.

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Michigan's Contaminant Induced Health Crisis

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Facing the Challenge of the Evolving Nature of Environmental Contamination

Prepared for the Director of the Michigan Department of Environmental Quality

Prepared By Robert Delaney and Dr. Richard DeGrandchamp

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ISSUE PAPER 1

DISTRIBUTION OF PERFLUOROALKYL CHEMICALS IN MICHIGAN'S ENVIRONMENT

By Robert Delaney

Issue

The environment and the human population of Michigan have been exposed to widespread perfluoralkyl chemical (PFC) contamination. The sources, nature, and extent of this contamination, as well as, the impacts on biota and humans in Michigan, can only be described in extremely general terms because of a severe lack of data from across the state. Risks to the general population and the environment are unknown.

Background

PFCs were created in the 1940s and have been increasing in use ever since that date. The forms of PFCs that are most familiar to the general public are Scotchguard® and Teflon®. However, PFCs are found in thousands of products and processes used in industry and are contained in countless consumer products. PFCs were thought to be biologically inactive and completely safe until recently when it was discovered that PFC contamination was increasing in biota and human populations around the globe (including highly isolated biota such as the mammals of the arctic). Subsequent toxicity testing of lab animals indicated that at least some of these PFCs were highly toxic even in small doses. PFCs bioaccumulate and biomagnify in various animal species, such as reptiles, mammals, fish and birds, and are also taken up in plants. Humans, at the top of the food web, can bioaccumulate high levels of various forms of PFCs.

Studies of exposed human populations have already shown diverse negative health effects (See, *Recent Epidemiology Studied Confirm Link Between PFC Exposure and Illness and Disease* (attached) Issue Paper 3). These negative health effects have been shown even at background levels of human blood serum contamination; levels that can be expected in the blood serum of the typical Michigan resident. The toxicity of PFCs will be covered in detail in a separate briefing memo.

PFCs have some unique characteristics that make them particularly difficult to deal with in the environment. Unlike most environmental contaminants, they cannot be broken down (as far as is known) through the normal biotic and abiotic processes that breakdown most contaminants. These chemicals do not photodegrade or biodegrade, are not oxidized, nor do they disassociate in water or other solvents. They are stable over a very large temperature range and are only destroyed by high temperature incineration. At this point, there is no known natural process that destroys PFCs in the environment. Thus, even if manufacturing of these chemicals is completely stopped, they will continue to be present in the environment and in human populations for the foreseeable future.

Of the approximately 400 PFCs, only perfluorooctane sulfonate (PFOS), the main PFC in the old formulation of Scotchguard®, and perfluorooctanoic acid (PFOA), the main PFC associated with Teflon®, have been the subjects of much toxicity testing. However, many of the 400 PFCs are in the environment, in biota and humans.

These chemicals are considered a significant threat to the environment and human health. The European Union has banned almost all uses of the longer chain PFCs (eight or more carbons in the PFC molecular backbone). In the United States (U.S.), the nine major producers of PFCs also agreed to voluntarily stop generating the longer chain PFCs. However, PFCs continue to be manufactured in other countries such as China and Brazil and are still used in many consumer products and manufacturing processes in the U.S.

There is relatively little data on PFC contamination in Michigan and the Great Lakes; however, some of the earliest studies were completed in Michigan. PFC contamination has been detected in each of the Great Lakes. In Lake Superior, PFCs were found throughout the water column, including the deepest portions of the lake. PFOA was consistently found to have the highest concentrations of the PFCs analyzed, and were generally 1.5 to 2 fold greater in concentration than PFOS. PFOA concentrations in Lake Superior water ranged from 0.07 to 1.2 parts per trillion (ppt). The two major sources of PFC contamination to the lake were air deposition and contamination entering from tributaries, with tributaries estimated to contribute over 55 percent of PFOA and PFOS (Scott, 2010). Boulanger et al., 2004, reported contamination in Lakes Erie and Ontario surface waters from 16 sampling locations. Concentrations ranged from 21 to 70 ppt for PFOS and 27 to 50 ppt for PFOA. These numbers are very significant given the volume of surface water in these two water bodies and the fact that it is possible that the groundwater/surface water criteria could be as low as 15 ppt for PFOS. The levels of PFOS also approach or exceed the tentative drinking water criteria being developed by the Michigan Department of Environmental Quality, Remediation Division. Current PFOA criteria is promulgated under Part 31, Water Resources Protection, of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended. Although the current PFOA criteria for surface water used as a drinking water source is 420 ppt, the surface water in these two bodies of water were approximately only one order of magnitude lower in concentration than the criteria (and higher than New Jersey's standard of 40 ppt). A mass balance study of the concentrations of eight PFCs in Lake Ontario revealed that the main sources of PFC contamination came from tributaries and inflow from Lake Erie. Air deposition of PFCs was not a main contributor to PFC concentrations (Boulanger et al., 2005).

There are at least three things that are critical to understand about these findings. First, given the dilution effects due to the enormous volumes of water in Lakes Erie and Ontario, these are very high concentrations of contamination. Secondly, there must be highly contaminated sources that are adding PFCs to the watersheds of these two lakes. Finally, it can be expected that with only 16 samples taken across two such large water bodies, there must be high concentration, localized contamination in the lakes, such as areas impacted by parts of the watersheds that are heavily industrialized. Ecological and human exposure in some areas might be exceedingly high in relation to tentative criteria.

Screening level sediment sampling was done from 2001 to 2005 on tributaries to the four Great Lakes that border Canada (map attached) (Anon., 2009). Sediment contamination was highest in tributaries that passed through highly urbanized areas. No sediment data is available for the Michigan portions of the watersheds of the Great Lakes, although, it is noteworthy that the highest levels of sediment contamination were found in the Detroit River. Impacted sediments will act as a continuing sink of PFC contamination to surface water into the future, even after discontinuation of PFC discharge to surface water. It also represents a pathway of continuing contamination to the food web of the Great Lakes.

Several studies have shown PFC contamination throughout the food web of the Great Lakes region. PFCs have been found in benthic algae, amphipods, zebra muscles, round gobies, Chinook salmon, lake trout, whitefish, small mouth bass, carp, mink, eagles, frogs, and snapping turtles (Kannan et al., 2005, attached). Kannan's studies (2002) demonstrated extremely high concentrations of PFCs in mink from the Kalamazoo River watershed. The attached article by Kannan (2005) gives a good overview of the widespread impact of PFCs on Michigan's ecosystem. Another important study of PFC contamination in Great Lakes' biota was published in 2011 on the 20 year trends of PFC concentrations in herring gull eggs from seven herring gull colonies (Gebbink, 2009). The concentrations of PFCs (PFOA and PFOS) that major U.S. producers had agreed to terminate manufacturing in the U.S were found to decrease in herring gull eggs over time; while the concentrations of analyzed PFCs still in production were found to increase.

Finally, Wurtsmith Air Force Base, located in Oscoda is the only point source of PFCs that has been documented in Michigan. Very high level contamination has been found at numerous locations on the base, and groundwater has been impacted over an area of approximately 5.7 square miles. Approximately 2.08 square miles of swamp and marsh, 9.37 miles of the Au Sable River, 2.89 miles of Van Ettan Creek, and 3.06 miles of Van Ettan Lake have been contaminated with PFCs from the base (map attached).

In 2011, wild fish tissue samples (fillets) were collected from a marsh just south of the base, and analyzed for 13 different PFCs. Seven different PFCs were detected in the fish. PFOS was the most frequently detected PFC and the PFC with the highest concentrations. The PFOS concentrations ranged from 334 to 9,580 nanograms per gram (344,000 to 9,580,000 ppt) wet weight in fish fillets. The levels of contamination in these fish averaged almost an order of magnitude higher than anything documented in the literature to date. At the moment, Michigan holds the dubious honor of having the most PFC contaminated fish reported in the literature from around the globe.

The PFC levels in these fish fillets were deemed to be so much higher than provisional heath-based reference values issued by the U.S. Environmental Protection Agency and the Minnesota Department of Health that an immediate "Do Not Eat the Fish" advisory was issued for the marsh and the Au Sable River south of the base. Those who have been eating fish out of Clarks Marsh, depending on their levels of consumption, likely have had extremely high levels of exposure to PFCs, and may have experienced those levels for more than a decade. Given the long half-lives of PFCs in humans (as long as eight years to eliminate half of the PFC from the body), some residents of Oscoda are likely to have very dangerous levels of PFCs in their blood.

At this time, no known human PFCs exposure data for Michigan residents has been published in the literature. However, the PFOA estimated median serum levels for the U.S. population is 4 parts per billion (ppb), and the estimated median serum level for PFOS is 21 ppb (Steenland, 2009). Michigan median serum levels can be expected to be similar to the national estimated levels for PFCs.

Analysis

In conclusion, contamination of the Great Lakes' waters and the extensive contamination of biota across Michigan indicate widespread contamination of the waters of the state by PFCs. Source contributions and human and ecological exposure cannot be characterized other than in

the most general terms because of a lack of monitoring across the state and in the human population.

Recommendations

Recommendations are provided in a separate document.

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June 18, 2012

Attachment

Attached References

Anonymous, "Binational framework for identifying substances of potential threat to the great lakes basin, test case: perfluorooctane sulfonate (PFOS), its salts and its precursors, (larger class: perfluorinated alkyl (PFA))," http://www.epa.gov /bns/reports/march2009/PFOS-PFOA0309.pdf, March 25, 2009.

K Kannan et al.,"Perfluorinated compounds in aquatic organisms at various trophic levels in a Great Lakes food chain," *Arch. Environ. Contam. Toxicol*., Vol. 48, 2005, pp. 559-566.

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K Kannan et al., "Perfluorooctane sulfonate and related fluorinated hydrocarbons in mink and river otters from the United States," *Environ. Sci. Technol.,* Vol. 36, No. 12, 2002, pp. 2566-2571.

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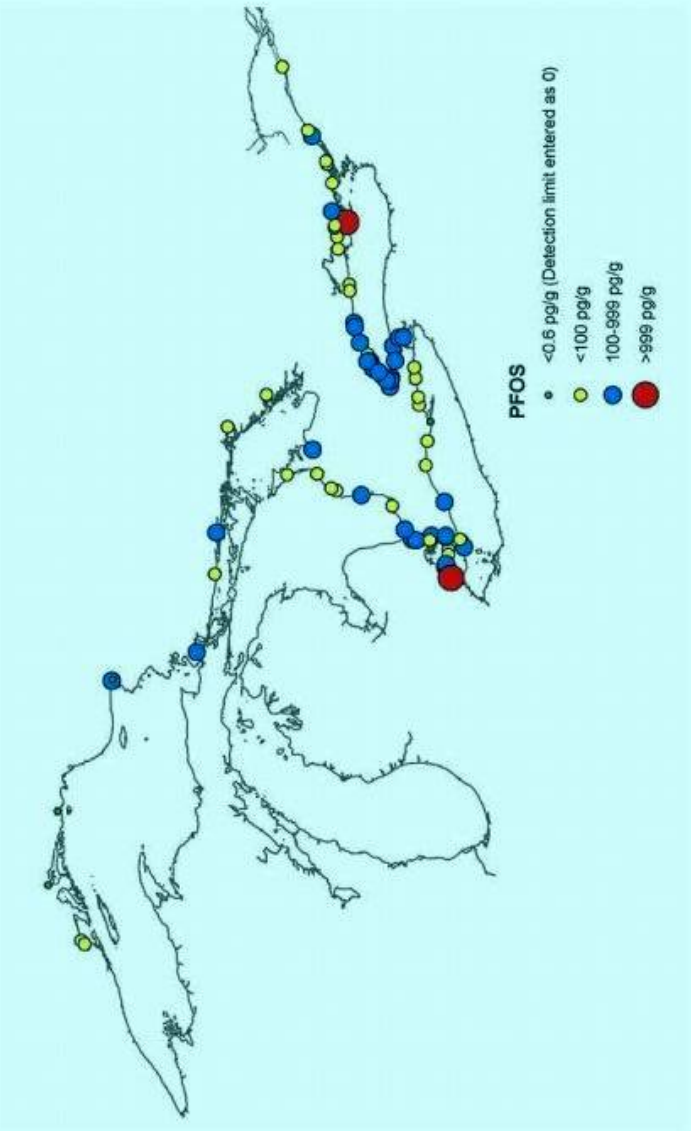
VI Furdui et al., "Spatial distribution of perfluoroalkyl contaminants in lake trout from the Great Lakes," *Environ. Sci. Technol.,* Vol. 41, No. 5, 2007, pp. 1554-1559.

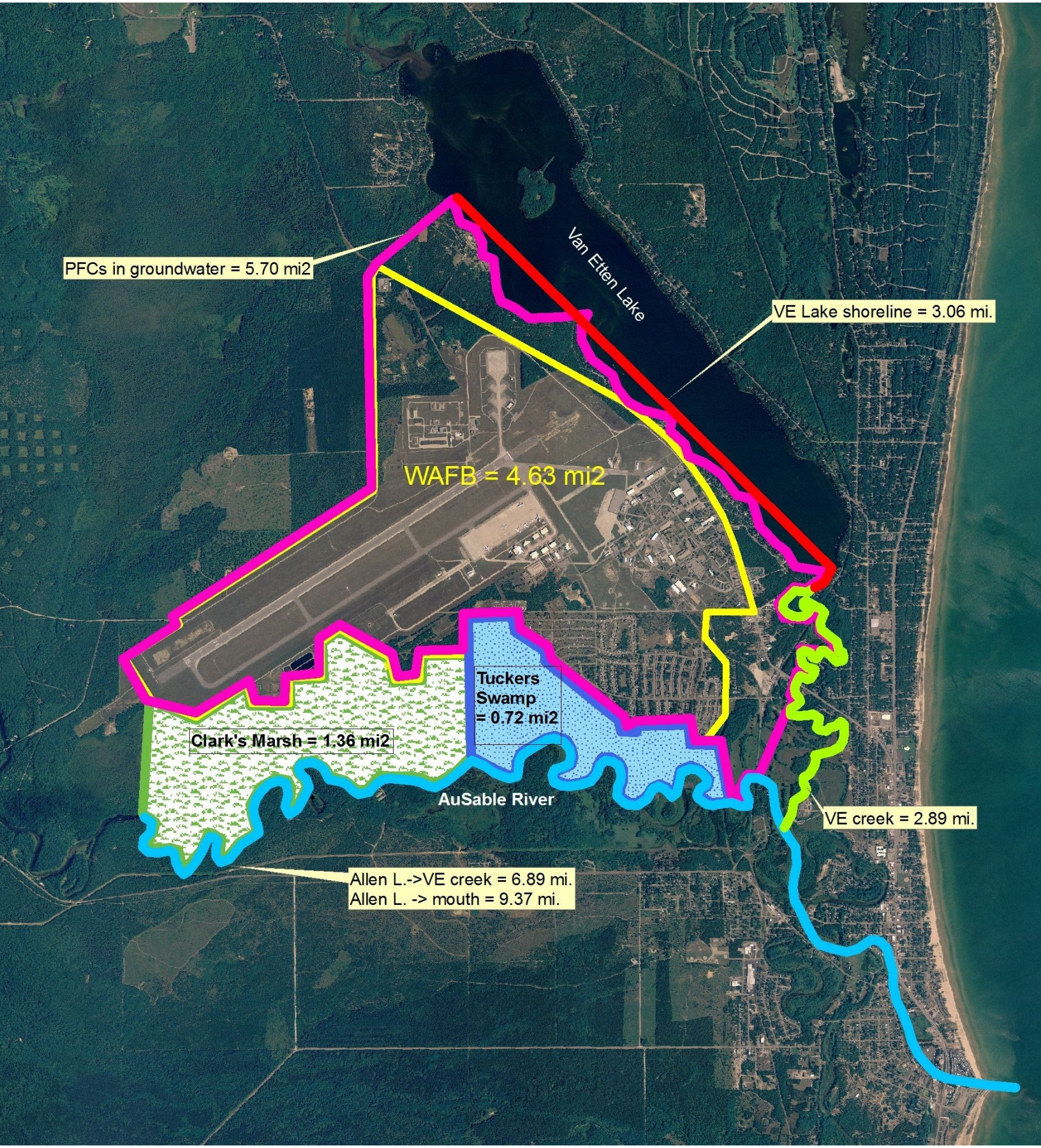
JP Giesy and K Kannan, "Global distribution of perfluorooctane sulfonate in wildlife," *Environ. Sci. Technol.,* Vol. 35, No. 7, 2001, pp. 1339-1342.

CA Moody et al., "Occurrence and persistence of perfluorooctane sulfonate and other perfluorinated surfactants in groundwater at a fire-training area at Wurtsmith Air Force Base, Michigan, USA," *J. Environ. Monit.,* Vol. 5, No. 2, 2003, pp. 341-345.

Levels of PFOS in Surficial Sediments of Canadian Tributaries to the Great Lakes, 2001-2005



Source: GLBTS 2006 Annual Progress Report


PFCs in groundwater = 5.70 mi2
Van Etten Lake
VE Lake shoreline = 3.06 mi.
WAFB = 4.63 mi2
Tuckers
Swamp
= 0.72 mi2
Clark's Marsh = 1.36 mi2
AuSable River
VE creek = 2.89 mi.
Allen L.->VE creek = 6.89 mi.
Allen L. -> mouth = 9.37 mi.

March 25, 2009

BINATIONAL FRAMEWORK FOR IDENTIFYING SUBSTANCES OF POTENTIAL THREAT TO THE GREAT LAKES BASIN

Test Case: Perfluorooctane Sulfonate (PFOS), its Salts and its Precursors, and Perfluorooctanonic Acid (PFOA)
(Larger Class: Perfluorinated Compounds (PFCs))

I. FEEDERS FOR SUBSTANCE IDENTIFICATION

National Chemical Management Programs

Canada

PFOS has been assessed CEPA toxic under the Canadian Environmental Protection Act (CEPA, 1999) and was added to CEPA 1999 Schedule 1- List of Toxic Substances in 2006.[1]

A key element of the Chemicals Management Plan (CMP) involves taking immediate action on five substance categories including PFOS.[2] The Canadian Government has proposed to prohibit uses of 50 PFOS substances because there is strong evidence that they pose a risk to the environment or human health.[3] PFOS is included in the monitoring plan for the CMP (either Year 1 or Year 2).[4]

PFOA (an 8 carbon PFCA) is currently being assessed by Environment Canada and Health Canada. A Draft Assessment Report could be published in spring or summer 2009. [5] Dependent on the conclusions within the final screening assessment report, risk management measures could be proposed
Environment Canada and Health Canada have put forward an Action Plan (*Perfluorinated Carboxylic Acids (PFCAs) and Precursors: An Action Plan for Assessment and Management)* in order to 'provide a broad perspective on the Departments' approach to PFCAs and their precursors'.[6]

United States

PFOS is not included in EPA's High Production Volume (HPV) Program. 3M, the principal global manufacturer of PFOS, working in partnership with EPA, announced in 2000 that it would voluntarily phase out production by the end of 2002. Following the voluntary phaseout of PFOS by 3M, EPA took prompt regulatory action on March 11, 2002,[7] and December 9, 2002,[8] by publishing two significant new use rules (SNURs) under the Toxic Substances Control Act (TSCA) to limit any future manufacture or importation of 88 PFAS chemicals specifically included in that phaseout. Furthermore, on October 9, 2007,[9] EPA published another SNUR on 183 additional PFAS chemicals. These SNURs recognized the continuation of a few specifically limited, highly technical uses of these chemicals for which alternatives were not available, and which were characterized by very low volume, low exposure, and low releases. Any other uses of these chemicals would require prior notice to and review by the USEPA.

The October 2007 SNUR allowed for one existing use of one PFOS salt as a mist suppressant in chromium plating, especially to promote compliance with a Clean Air Act MACT standard and the OSHA permissible exposure limit (PEL) for hexavalent chromium. The preamble to the final rule

noted EPA's concern about ongoing PFOS releases to wastewater, and the Agency's interest in ways to minimize and/or prevent these releases.

PFOA is not included in EPA's HPV Program.

Great Lakes Monitoring and Surveillance
There are specific PFOS substances (and its salts) common with the Great Lakes Screening Project. These include:[10]

CAS #	Chemical Name
1691-99-2	1-Octanesulfonamide, N-ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-(2-hydroxyethyl)-
2795-39-3	1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-, potassium salt
2991-51-7	Glycine, N-ethyl-N-[(heptadecafluorooctyl)sulfonyl]-, potassium salt
4151-50-2	1-Octanesulfonamide, N-ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-
24448-09-7	1-Octanesulfonamide, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-(2-hydroxyethyl)-N-methyl-
31506-32-8	1-Octanesulfonamide, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-methyl-
25268-77-3	2-Propenoic acid, 2-[[(heptadecafluorooctyl)sulfonyl]methylamino]ethyl ester
38006-74-5	1-Propanaminium, 3-[[(heptadecafluorooctyl)sulfonyl]amino]-N,N,N-trimethyl-, chloride
57589-85-2	Benzoic acid, 2,3,4,5-tetrachloro-6-[[[3-[[(heptadecafluorooctyl)sulfonyl]oxy]phenyl]amino]carbonyl]-, monopotassium salt
67969-69-1	1-Octanesulfonamide, N-ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-[2-(phosphonooxy)ethyl]-, diammonium salt
68298-11-3	1-Propanaminium, 3-[[(heptadecafluorooctyl)sulfonyl](3-sulfopropyl)amino]-N-(2-hydroxyethyl)-N,N-dimethyl-,hydroxide, inner salt
68891-96-3	Chromium, diaquatetrachloro[μ-[N-ethyl-N-[(heptadecafluorooctyl)sulfonyl]glycinato-O':O"]]μ-hydroxybis(2-methylpropanol)di-
68608-14-0	Sulfonamides, C4-8-alkane, perfluoro, N-ethyl-N-(hydroxyethyl),reaction products with 1,1'-methylenebis[4-isocyanatobenzene]
307-35-7	1-Octanesulfonyl fluoride, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-
376-14-7	2-Propenoic acid, 2-methyl-, 2-[ethyl[(heptadecafluorooctyl)sulfonyl]amino]ethyl ester
14650-24-9	2-Propenoic acid, 2-methyl-, 2-[[(heptadecafluorooctyl)sulfonyl]methylamino]ethyl ester
179005-06-2	Sulfonamides, C4-8-alkane, perfluoro, N-[3-(dimethyloxidoamino)propyl], potassium salts
1763-23-1	1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-

The Canadian Management Plan Monitoring Program for 2009-2010 will be monitoring PFOA in the Great Lakes. Sediments, aquatic biota, air/precipitation, wildlife and wastewater/biosolids will be monitored for PFOA.[11]

PFOA substances on the Domestic Substances List (substances that are currently in commerce or in use in Canada) are listed in the table below.

PFOA substances on Canada's Domestic Substances List (DSL) [12]

CAS #	Chemical Name
3825-26-1	Octanoic acid, pentadecafluoro-, ammonium salt
53515-73-4	2-Propenoic acid, 2-methyl-, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyl ester, polymer with 2-propenoic acid
68187-42-8	Propanamide, 3-[(γ-ω-perfluoro-C_{4-10}-alkyl)thio] derivatives
95370-51-7	Carbamic acid, [2-(sulfothio)ethyl]-, C-(γ-ω-perfluoro-C_{6-9}-alkyl) esters, monosodium salts
678-39-7	1-Decanol, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro

Other Sources of Information

Organization for Economic Co-operation and Development (OECD)

In 2000, several member countries collected information on the environmental and human health hazards of PFOS to produce a hazard assessment report.[13] The report concluded that PFOS's persistence, its presence in the environment and in a number of wildlife species, and bioaccumulation potential are a cause for concern.[14]

European Union

In 2007 EU measures were adopted introducing legislation across Europe restricting PFOS. The new restrictions became effective June 27, 2008.[15]

The EU also published Directive 2006/122/EC on December 27, 2006, which states that PFOS and related substances shall not be placed on the market according to the following restrictions:[16]

- in concentrations equal to or higher than 0.005% by mass as a substance or constituent of preparations;
- in semi-finished products or products, or parts thereof, at a level of 0.1% by mass; and
- in textiles or other coated materials in which the amount of PFOS will be equal to or higher than 1 $\mu g/m^2$ of the coated material.

Australia

In Australia, there has been a voluntary phase-out agreement for PFOS since 2000.[17]

Norway

In April 2005, Norway proposed major reductions in emissions of PFOS by 2010.
The Norwegian Pollution Control Authority has adopted new legislation on PFOS in textiles, firefighting foams and impregnating agents. The new law came into force on July 1, 2007. Norway has laid down the same limits for the use of PFOS as the EU.[18]

Norway announced in December 2007 that the discharges of PFOA should be significantly reduced by 2010 and eliminated before 2020. The Norwegian Pollution Control Authority

commissioned a survey of national sources of PFOA and PFOA-precursors in Norway. They have committed to identify all possible sources of PFOA in Norway along the whole life cycle from production, use and disposal in industrial manufacturing and applications and other possible sources such as long range transport by air and sea currents.[19]

Sweden
In 2005, Sweden proposed PFOS and 96 PFOS-related substances as candidates for the Stockholm Convention on Persistent Organic Pollutants (POPs). A draft risk management evaluation was prepared for discussion at the third meeting of the POPRC (November 2007) recommending listing PFOS under the Annex A of the Convention in order to eliminate or restrict production and use. It is expected that this recommendation will be put forward for decision at the 4th Conference of the Parties in *May 2009*.[20]

United Nations Economic Commission for Europe (UNECE)
In December 2005, the Parties to the United Nations Economic Commission for Europe (UNECE) Long-Range Transboundary Air Pollution (LRTAP) Convention's Protocol on POPs agreed that PFOS should be considered as a persistent organic pollutant. The convention explored management strategies in 2006.[21]

United States
The Minnesota Pollution Control Agency and Department of Health have undertaken significant work with respect to PFC contamination in Minnesota. See http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/index.html and http://www.pca.state.mn.us/cleanup/pfc/index.html.

II. CONSIDERATIONS FOR SUBSTANCE SELECTION

Monitoring and Surveillance
Numerous monitoring and surveillance data are available which demonstrates the presence of PFOS (and related substances (PFA)) in the Great Lakes Basin. For example:

- Furdui *et al.* 2007, "Spatial Distribution of Perfluoroalkyl Contaminants in Lake Trout from the Great Lakes".[22]
  - Reports perfluoroalkyl contaminant concentrations in Lake Trout from the Great Lakes.
  - Lowest average concentration of ΣPFC found in samples from Lake Superior (13 ± 1 ng g^{-1}). Highest average concentration found in samples from Lake Erie (152 ± 14 ng g^{-1}). Samples from Lake Ontario (60 ± 5 ng g^{-1}) and Lake Huron (58 ± 10 ng g^{-1}) showed similar average ΣPFC concentrations.
  - The major perfluoroalkyl contaminant observed was perfluorooctane sulfonate (PFOS) with the highest concentration found in samples from Lake Erie (121 ± 14 ng g^{-1}), followed by samples from Lake Ontario (46 ± 5 ng g^{-1}), Lake Huron (39 ± 10 ng g^{-1}), Lake Michigan (16 ± 3 ng g^{-1}), and Lake Superior (5 ± 1 ng g^{-1}).

- Martin *et al.* 2004, "Perfluoroalkyl Contaminants in the Lake Ontario Food Web".[23]

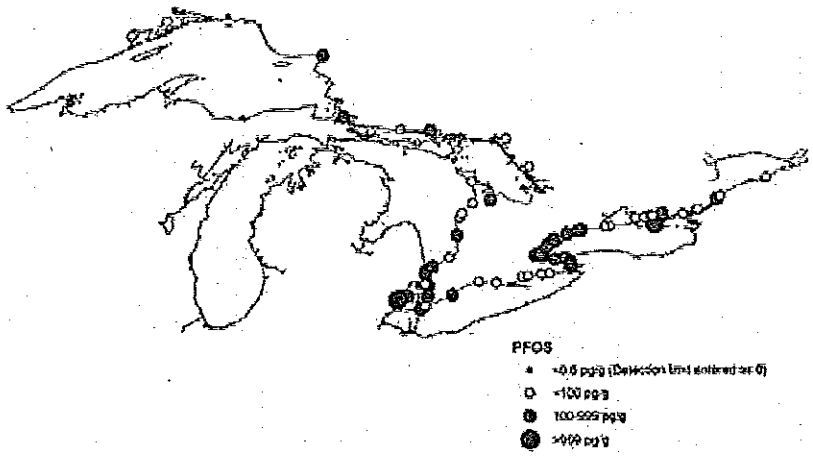
- Reports concentrations of PFOS in various organisms from a food web of Lake Ontario.
- The highest levels were found in polar bear, with a mean level of 3100 ng/g from seven animals (maximum value > 4000 ng/g). The concentrations of PFOS in polar bear are 5-10 times higher than the concentration of all other perfluoroalkyl substances and were higher than any other previously reported concentrations of persistent organochlorine chemicals in polar bear fat.

- Boulanger *et al.* 2004, "Detection of perfluorooctane surfactants in Great Lakes water".[24]
  - Reports concentrations of perfluorooctane surfactants from 16 water samples from Lakes Erie & Ontario.
  - Concentrations of PFOS in the two lakes ranged from 21-70 ng/L.
  - Concentrations of PFOA in the two lakes ranged from 27-50 ng/L, respectively.
  - Analysis also showed the presence of PFOS and PFOA precursors in both lakes, N-EtFOSAA (range of 4.2-11 ng/L) and FOSA (range of 0.6-1.3 ng/L), in all samples above the LOQ.
  - PFOSulfinate, another precursor, was identified at six of eight locations with a concentration range, when present, of <2.2-17 ng/L.
  - These are the first reported concentrations of perfluorooctane surfactants in Great Lakes water and the first report of PFOS precursors in any water body.

- Sinclair *et al.* 2006, "Occurrence of Perfluoroalkyl Surfactants in Water, Fish, and Birds from New York State".[25]
  - Analyzed concentrations of PFOS and several other perfluoroalkyl surfactants (PASs) in nine major water bodies in New York State.
  - Elevated levels of PFOA were found in the Hudson River.
  - PFOS was the most abundant perfluorinated compound in all fish and bird liver samples.
  - Overall average concentrations of PFOS in fish were 8850-fold greater than that in surface water.

- Environment Canada June 2006, "Ecological Screening Assessment Report on Perfluorooctane Sulfonate, Its Salts and Its Precursors that Contain the $C_8F_{17}SO_2$, $C_8F_{17}SO_3$ or $C_8F_{17}SO_2N$ Moiety.[26]
  - Reports concentrations of PFOS in air, water, sediment & biota.
  - Information available at: http://www.ec.gc.ca/CEPARegistry/documents/subs_list/PFOS_SAR/PFOS_P5.cfm, (section 3.0 Environmental Concentrations).

- Concentrations of PFOS collected in a screening-level survey of recently deposited sediments in Canadian Great Lakes tributaries from 2001 to 2005 indicated relatively low PFOS concentrations that appear to be indicative of land use (i.e., elevated levels are generally found in more populated watersheds) (see figure below).[27]



Levels of PFOS in Surficial Sediments of Canadian Tributaries to the Great Lakes, 2001-2005

The four following published studies examined concentrations of PFOA in different Great Lakes locations. These studies represent the publicly available Canadian data on PFOA concentration in the Great Lakes water.

PFOA concentrations in water in the Great Lakes

Sampling Location (Year)	PFOA Identity	Concentration (µg/L)	No. of Samples	Detection Limit (µg/L)	Reference
Toronto, ON	PFOA	0.007–0.055	NA	0.001	Crozier et al. (2005)[28]
Etobicoke Creek, ON (2002) (AFFF Spill)	Conjugate base	<0.009–11.3 (Measured in surface water)	61	0.009	Moody et al. (2002)[29]
Algoma, ON (2001)	Conjugate base	<0.0005–0.004 (Measured in rainwater)	16	0.0005	Scott et al. (2003)[30]
Lake Erie (August 7–12, 2003)	PFOA, ammonium salt	0.021–0.047	8	0.000 013	Boulanger et al. (2004)[31]
Lake Ontario (August 7–12, 2003)	PFOA, ammonium salt	0.015–0.070	8	0.000 013	Boulanger et al. (2004)[32]

Environmental Levels and Trends
For environmental levels, please see monitoring and surveillance data.

Retrospective analyses of archived lake trout samples from Lake Ontario have identified a 4.25-fold increase (from 43 to 180 ng/g wet weight, whole fish) from 1980 to 2001.[33]

A summary of studies of fluorinated surfactants in the Great Lakes environment is presented in Appendix A.

Source/Use/Release/Exposure Information
Source/use/release/exposure information available primarily from Environment Canada's *Perfluorooctane Sulphonate (PFOS), Its Salts and Its Precursors Risk Management Strategy*.[34]

Source/Use
PFOS, its salts and its precursors are not manufactured in Canada but rather are imported as chemicals or products from the United States for Canadian uses. The principal applications of PFOS and its precursors were for water, oil, soil and grease repellents for use on rugs, carpets, fabric and upholstery, and in food packaging, as well as specialized chemical applications such as fire-fighting foams, hydraulic fluids, carpet spot removers, mining and oil well surfactants and other specialized chemical formulations. In Canada, in the past, PFOS substances were typically imported as raw chemicals and in products and formulations.

An Environment Canada use pattern survey undertaken in 2000 indicated that, from 1997 to 2000, an estimated 318 tonnes of PFOS substances were used in Canada.

Background information collected in support of the PFOS Regulations indicated that, since 2002, imports into Canada of PFOS as raw chemicals and in products or formulations have essentially ceased. This finding was confirmed by a use pattern survey published on January 15, 2005.

The 2005 survey results indicated that there are no manufacturers or exporters of PFOS in Canada, that approximately three tonnes of PFOS were imported in 2004 for use as a surfactant in fume suppressants for the metal plating sector, and that it is very likely that most inventories of PFOS in all other sectors have been depleted, except for an estimated 300 tonnes of stock piled fire fighting foams.

PFOA is used to make fluoropolymers, substances with special properties that have thousands of important manufacturing and industrial applications in almost all industry segments, including the aerospace, automotive, building/construction, chemical processing, electrical and electronics, semiconductor, and textile industries. Consumer products made with fluoropolymers include non-stick cookware and breathable, all-weather clothing.

PFOA may be a breakdown product of some fluorotelomers, which are used as surface application treatments on carpets, textiles, paper, leather, and construction materials to provide water, stain, grease, and soil resistance properties. Fluorotelomers may also be used as surfactants in cleaning and coating products.

Globally, there are eight major manufacturers of PFOA. 3M, the original manufacturer of PFOA, has phased out PFOA production in the U.S. Dyneon, a 3M subsidiary in Europe that continues to use PFOA, has announced plans to discontinue the use of PFOA by the end of 2008.

Release

PFOS, its salts and its precursors may enter the environment through treated or untreated municipal/industrial wastewater discharges to surface water and through leachates from landfills when products and materials containing these substances are sent for final disposal. PFOS may also be released directly to air, land, and surface water when products containing PFOS are used.

PFOA may be released during fluoropolymer and fluorotelomer manufacturing.

Exposure

Exposure in the Canadian environment likely results from the release, transformation, and movement of PFOS and its precursors in effluents and fugitive emissions from manufacturing sites elsewhere in the world, and releases from industrial and municipal wastewater effluents.

PFOA has been detected in the blood of the general U.S. population, although it is not fully understood how individuals are exposed to the chemical. Occupational exposures have been documented at manufacturing facilities.

Environmental Benchmarks

A few states have established environmental quality benchmark criteria. No benchmarks are available from Canada. EPA and the United Kingdom have issued criteria for PFOS and PFOA in drinking water.

States
Minnesota has issued a Health Risk Limit for PFOS (0.3 ug/L) and PFOA (0.5 ug/L) in drinking water, and fish contaminant advisories for several highly impacted bodies of water. Minnesota is also considering effluent limits for perfluorinated compounds (PFCs) in wastewater. Two other states, New Jersey and North Carolina, also regulate PFCs in drinking water.

United States
On January 8, 2009, EPA's Office of Water issued Provisional Health Advisories for PFOA and PFOS to assess potential risk from exposure to these chemicals through drinking water. EPA used the exposure scenario of a 10-kg child consuming 1 L/day of drinking water to calculate Provisional Health Advisories of 0.4 µg/L (ppb) for PFOA and 0.2 µg/L (ppb) for PFOS.[1]

United Kingdom
The Health Protection Agency advises that the maximum acceptable concentration of PFOS in drinking water is 0.3 µg/L. The maximum acceptable concentration of PFOA in drinking water is 10 µg/l.[35]

Environmental and Health Data
Information on health data can be found from Health Canada's State of the Science Report for a Screening Health Assessment for PFOS (July 2006).[36]

The final ecological screening assessment report concludes that PFOS, its salts and its precursors are considered to meet the criteria set out in section 64(a) of CEPA 1999. The draft 2004 human health screening assessment report concludes that PFOS, its salts and its precursors do not meet the criteria set out in section 64(c) of CEPA 1999.[37]

The U.S. Centers for Disease Control (CDC) published a study in 2007 which reported significant reductions in human blood concentrations of PFOS and PFOA from 1999 to 2000 compared to the most recent 2003-2004 data. The geometric mean for PFOA in human blood was reduced by 25 percent over this period, and PFOS was reduced by 32 percent. The report concluded that these reductions were most likely related to changes brought about by EPA efforts on these chemicals and other related efforts by government and industry.

EPA prepared and submitted a *Draft Risk Assessment of the Potential Human Health Effects Associated With Exposure to Perfluorooctanoic Acid and Its Salts (PFOA)* to the EPA Science Advisory Board (SAB) for peer review in 2005. Most of SAB Panel members agreed that PFOA cancer data are consistent with the EPA guidelines descriptor 'likely to be carcinogenic to humans'.

[1] U.S. EPA. 2009. Provisional Health Advisories for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS). Available at http://www.epa.gov/waterscience/criteria/drinking/pha-PFOA_PFOS.pdf. Accessed: February 24, 2009.

EPA is still in the process of evaluating this information and has not made any definitive conclusions regarding potential risks, including cancer, at this time.

Available data suggests that PFOA and its salts are not genotoxic, but are tumourigenic in rats and immunotoxic in mice. PFOA and its salts show reproductive and developmental toxicity in rodents as well as moderate to high subchronic oral toxicity in rodents and monkeys after long term exposure by oral route.[38] PFOA and other perfluorinated substances have been found in human blood at a global scale. PFOA has also been detected in seminal plasma, breast milk and umbilical cord blood.[39]

Other Reasons for Concern
Evidence suggests that PFOS has endocrine disrupting properties in rats.[40]

III. PRESENT MANAGEMENT STATUS

Canada
On December 16, 2006, the proposed Perfluorooctane Sulfonate and Its Salts and Certain Other Compounds Regulations were published in the *Canada Gazette*, Part I. The final Regulations were published in Part II of the *Canada Gazette* on June 11, 2008. The Regulations prohibit the manufacturing, use, selling, offering for sale or importing PFOS and its salts and certain other compounds; with some exceptions. More information on this regulation can be found at: http://gazetteducanada.gc.ca/partII/2008/20080611/html/sor178-e.html.[41]

Because PFOA is currently being assessed by Environment Canada and Health Canada, the PFOA management status is not yet determined. However, as set out in the *Action Plan for the Assessment and Management of Perfluorinated Carboxylic Acids and their Precursors* published in June 2006 in the *Canada Gazette,* the Government has sought action from industry through a voluntary agreement to significantly reduce residual PFCA precursors that are present in certain substances already in Canadian commerce. The Government worked diligently with stakeholders to establish details for this action, including timelines, reduction targets and an accountability framework and is calling for voluntary actions on substances for which assessments are underway and not yet published

The draft Performance Agreement aligns with a similar stewardship program run by the United States Environmental Protection Agency (USEPA). The voluntary proposed agreement was published for public comment on January 30, 2009.

United States
The SNURs require manufacturers and importers to notify the EPA at least 90 days before new manufacture or import of these substances. This provides the EPA with the necessary time to evaluate the intended new use and prohibit or limit the new activity if necessary. The three SNURs for PFAS chemicals (discussed in Section I) essentially restrict all manufacture and importation, with the exception of PFOS salt used as a mist suppressant in chromium plating.[42]

EPA Region 5 recently completed a field survey of wastewater at chromium plating facilities in both Chicago and Cleveland to determine the extent of PFC releases to wastewater from this

authorized use. The survey results will be summarized and submitted to EPA Office of Air Quality Planning and Standards under the CAA residual risk analysis for the Chromium MACT, in order to inform the rulemaking with respect to the metal finishing source category.

EPA has also engaged the National Association of Surface Finishers, beginning some dialogue on the development of alternative compounds and best management practices to minimize and/or prevent PFOS releases. Future activities are being determined at this time, pending guidance from EPA Region 5.

EPA continues to work on a TSCA Risk Assessment for PFOA. A *Draft Risk Assessment of the Potential Human Health Effects Associated With Exposure to Perfluorooctanoic Acid and Its Salts (PFOA)* underwent a peer review by the EPA Science Advisory Board (SAB), and the Final SAB Report is available at http://www.epa.gov/oppt/pfoa/pubs/pfoarisk.htm. EPA expects to conduct a second SAB review upon completion of a final risk assessment.

EPA has a robust Safe Drinking Water Act (SDWA) settlement with DuPont with respect to a significant drinking water contamination problem in the Ohio River Valley, near DuPont's Washington Works in Parkersburg, WV.

In 2005, under TSCA EPA entered into two enforceable consent agreements with industry for laboratory-scale incineration testing of fluoropolymers and fluorotelomers to help determine whether products made or treated with these chemicals may produce PFOA when they are disposed of in municipal incinerators.

EPA, in collaboration with industry, is gathering more information about PFOA through Memoranda of Understanding (MOUs). In 2004, EPA signed an MOU with 3M and Dyneon LLC for monitoring in the vicinity of a fluoropolymer manufacturing facility in Decatur, AL. In 2005, EPA and DuPont entered into an MOU entitled *PFOA Site-Related Environmental Assessment Program* to conduct a screening level exposure assessment to characterize exposure and releases at DuPont's Washington Works Facility in West Virginia.

In January 2006, EPA negotiated the PFOA Stewardship Program with the eight major companies in the industry. The PFOA Stewardship Program commits the eight companies to voluntary reductions of facility emissions and product content of PFOA and related chemicals by 95% no later than 2010, and to work toward the elimination of emissions and product content by 2015. In 2008 annual progress reports for the PFOA Stewardship Program, four of the eight companies had met the 95% reduction commitment for PFOA emissions and had significantly reduced product content from U.S. operations, and one company had no U.S. operations. Corporate strategies to meet the program's goals included control/treatment technologies, process changes, product reformulation, and new chemical development. For example, 3M has developed new technologies—with favorable environmental, health and safety characteristics—that enable the company to reformulate many of the products affected by the PFOA phase out. Several other companies have also announced plans to introduce new chemicals that do not include PFOA and

cannot breakdown to PFOA in the environment.[2] More information about the PFOA Stewardship Program is available at EPA's PFC web site (http://www.epa.gov/oppt/pfoa/index.htm), and in electronic dockets at http://www.regulations.gov.

[2] Krasnic, T. 2009. *2010/15 PFOA Stewardship Program Overview and Update*. Presented at EPA Workshop on Managing Perfluorinated Chemicals and Transitioning to Safer Alternatives, Geneva, Switzerland. 12-13 February, 2009.

APPENDIX A
Fluorinated Surfactants in the Great Lakes Environment - Published Studies

1. "Monitoring perfluorinated surfactants in biota and surface water samples following an accidental fire-fighting foam release into Etobicoke Creek." C.A. Moody, J.W. Martin, W.C. Kwan, D. C. G. Muir and S. A. Mabury. Environmental Science & Technology. 2001; 36: 545-551. Fluorinated Surfactants\Moody et.al. 2002.pdf.

   Summary: This study measured concentrations of perfluorinated surfactants released by a spill in Etobicoke Creek, a tributary of Lake Ontario. Measurements from surface waters and fish livers were taken. The study suggested that perfluorinated surfactants will persist and bioaccumulate following release into the aquatic environment.

2. "Detection of perfluorooctane surfactants in Great Lakes water." B. Boulanger, J. Vargo, J.L. Schnoor, K.C. Hornbuckle. Environmental Science & Technology. 2004; 38,(15): 4064-70. Fluorinated Surfactants \Boulanger et. al. 2004.pdf

   Summary: This study analyzed for perfluorooctane surfactants from sixteen sites in Lake Erie and Ontario. Concentrations of PFOS and PFOA in the two lakes ranged from 21-70 and 27-50 ng/L, respectively. Precursors to these compounds were also measured in both lakes.

3. "Perfluorinated compounds in aquatic organisms at various trophic levels in a Great Lakes food chain." K. Kannan, L. Tao, E. Sinclair, S.D. Pastva, D.J.Jude and J.P. Giesy. Archives of Environmental Contamination and Toxicology. 2005; 48 (4): 559-66. Fluorinated Surfactants\Kannan et.al. 2005.pdf

   Summary: Trophic transfer of perfluorooctane sulfonate (PFOS) and other related perfluorinated compounds were examined in a Great Lakes benthic food web. Concentrations of perfluorooctane sulfonate were measured in tissue from various organisms including water–algae–zebra mussel–round goby–smallmouth bass. PFOS was most widely detected in benthic organisms at various trophic levels. This study calculated the bioaccumulation factor in benthic invertebrates to be 1000, while biomagnification factors in larger predators like bald eagles and minks to be 10 to 20 times that of their prey.

4. "Mass budget of perfluorooctane surfactants in Lake Ontario." B. Boulanger , A. M Peck , J. L Schnoor , K. C Hornbuckle. Environmental

Science & Technology. 2005; 39, (1):74-79 Fluorinated Surfactants \Boulanger et.al. 2005.pdf

Summary: A mass budget was done on eight perfluorooctane surfactants in Lake Ontario. The study showed inflow from Lake Erie as well as waste water treatment plants are the two major sources of perfluorooctane surfactants into Lake Ontario. Outflow through the St. Lawrence River is the major loss mechanism. This study also measured perfluorooctane surfactants on particulate matter in the air.

5. "Spatial Distribution of Perfluoroalkyl Contaminants in Lake Trout from the Great Lakes." V. I. Furdui, N. L. Stock, D. A. Ellis, C. M. Butt, D. M. Whittle, P. W. Crozier, E. J.Reiner, D. C. G. Muir and S. A. Mabury. Environmental Science & Technology. 2007; 41(5); 1554-1559. Fluorinated Surfactants\Furdui et.al. 2007.pdf.

Summary: This study measured concentrations of perfluorinated carboxylates (PFCAs) and perfluorinated sulfonates (PFSAs) in 4 year-old lake trout in all five Great Lakes. Results showed that the highest average concentrations were found in Lake Erie, followed by Lake Ontario and Huron, with Lake Michigan and Superior having the lowest concentrations respectively. Data also showed the major contributor to the sum concentrations of perfluorinated carboxylates (PFCAs) was from PFOA.

6. "Perfluoroalkyl Contaminants in a Food Web from Lake Ontario." J. W. Martin, D. M. Whittle, D. C. G. Muir and S. A. Mabury. Environmental Science & Technology. 2004; 38(20); 5379-5385. Fluorinated Surfactants\Martin et.al. 2004.pdf

Summary: This study analyzed PFOS, the homologous series of PFCAs, and the PFOS-precursor heptadecafluorooctane sulfonamide (FOSA) in various organisms from a food web of Lake Ontario. The highest mean concentration was found in benthic organisms at the lowest trophic level, since these organisms are foraged on by larger fish, there is potential for biomagnification. Bioaccumulation in larger fish was also shown in this study.

7. "Occurrence of Perfluoroalkyl Surfactants in Water, Fish, and Birds from New York State." E. Sinclair, D.T. Mayack, K. Roblee, N. Yamashita and K. Kannan. Archives of Environmental Contamination and Toxicology. 2006; 50, (3): 398-410. Fluorinated Surfactants\Sinclair et.al. 2006.pdf.

Summary: This study determined concentrations of perfluorooctanesulfonate (PFOS) and several other perfluoroalkyl surfactants (PASs) in nine major water bodies in New York State. Elevated levels of PFOA were found in the Hudson River. PFOS were the most abundant perfluorinated compound in all fish and bird liver samples, and overall average concentrations of PFOS in fish were 8850-fold greater than that in surface water.

8. "Perfluorinated Compounds in the Great Lakes" Persistent Organic Pollutants in the Great Lakes, Handbook in Environmental Chemistry, Vol. 5, Part N, pp. 391-438, Springer-Verlag: Berlin & Heidelberg, Germany (2006), R. A. Hites, editor.

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[7] 67 FR 11007, March 11, 2002. http://www.epa.gov/fedrgstr/EPA-TOX/2002/March/Day-11/t5746.htm.

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[10] Compared: List of PFOS, its Salts and its Precursors, Appendix 1 of *PERFLUOROOCTANE SULFONATE (PFOS), ITS SALTS AND ITS PRECURSORS RISK MANAGEMENT STRATEGY.* June 2006. Available online at: http://www.ec.gc.ca/CEPARegistry/documents/part/PFOS/app1.cfm. To: *Excel file: EPA Report Table_SRC (*Muir, D.C., Howard, P.H. and Meylan, W. 2007. Project: Screening Chemicals in Commerce to Identify Possible Persistent and Bioaccumulative (P&B) Chemicals in the Great Lakes.)

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Perfluorinated Compounds in Aquatic Organisms at Various Trophic Levels in a Great Lakes Food Chain

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Abstract. Trophic transfer of perfluorooctanesulfonate (PFOS) and other related perfluorinated compounds was examined in a Great Lakes benthic foodweb including water–algae–zebra mussel–round goby–smallmouth bass. In addition, perfluorinated compounds were measured in livers and eggs of Chinook salmon and lake whitefish, in muscle tissue of carp, and in eggs of brown trout collected from Michigan. Similarly, green frog livers, snapping turtle plasma, mink livers, and bald eagle tissues were analyzed to determine concentrations in higher trophic-level organisms in the food chain. PFOS was the most widely detected compound in benthic organisms at various trophic levels. Concentrations of PFOS in benthic invertebrates such as amphipods and zebra mussels were approximately 1000-fold greater than those in surrounding water, which suggested a bioconcentration factor (BCF; concentration in biota/concentration in water) of 1000 in benthic invertebrates. Concentrations of PFOS in round gobies were two- to fourfold greater than those in their prey organisms such as zebra mussels and amphipods. Concentrations of PFOS in predatory fishes (Chinook salmon and lake whitefish) were 10 to 20-fold greater than those in their prey species. Concentrations of PFOS in mink and bald eagles were, on average, 5- to 10-fold greater than those in Chinook salmon, carp, or snapping turtles. Because of the accumulation of PFOS in liver and blood, the biomagnification factor (BMF) of perfluorinated compounds in higher trophic-level organisms such as salmonid fishes, mink, and eagles were based on the concentrations in livers or plasma. Overall, these results suggest a BCF of PFOS of approximately 1000 (whole-body based) in benthic invertebrates, and a BMF of 10 to 20 in mink or bald eagles, relative to their prey items. Eggs of fish contained notable concentrations of PFOS, suggesting oviparous transfer of this compound. PFOA was found in water, but its biomagnification potential was lower than that of PFOS.

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Perfluorooctane sulfonate (PFOS), a fluorinated organic contaminant, has been the subject of many recent investigations (Hansen *et al.* 2001; Kannan *et al.* 2001a,b; Kannan *et al.* 2002a,b,c,d; Moody *et al.* 2002; Van de Vijver *et al.* 2003; Martin *et al.* 2004; Stock *et al.* 2004). Widespread distribution of PFOS in wildlife tissues collected from several regions of the globe has been reported (Giesy and Kannan 2001, 2002; Martin *et al.* 2004). Additional perfluorinated organic contaminants, such as perfluorohexanesulfonate (PFHS), perfluorooctanoate (PFOA), and perfluorooctanesulfonamide (PFOSA) have been reported to occur in the environment, although at lower concentrations and frequencies than PFOS. Earlier studies have suggested that concentrations of PFOS tend to be higher in predatory organisms than in lower trophic-level organisms of aquatic food chains (Kannan *et al.* 2002c). For instance, fish-eating birds (e.g., bald eagles) and mammals (e.g., mink) contained some of the highest concentrations of PFOS reported thus far. Nevertheless, earlier studies measuring concentrations of PFOS in biota have focused primarily on higher trophic-level organisms. Studies reporting the occurrence of PFOS in aquatic organisms at lower trophic levels in a food chain are scanty. In order to determine the biomagnification potential of PFOS in aquatic food webs, we need to measure concentrations in organisms at various trophic levels. In this study, we have measured concentrations of PFOS, PFHS, PFOA, and PFOSA in water, benthic algae, amphipods, zebra mussel (*Dreissena polymorpha*), crayfish, round gobies (*Neogobius melanostomus*), and smallmouth bass (*Micropterus dolomieui*) collected from three riverine locations. This represents a characteristic benthic food chain of the Great Lakes since the invasion of the Great Lakes by zebra mussels in the late 1980s; and by round gobies in the early 1990s (Hanari *et al.* 2004).

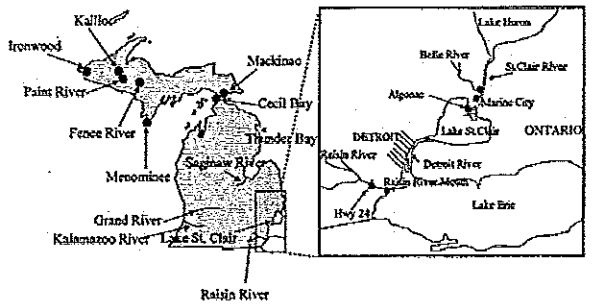

Fig. 1. Map of Michigan showing sampling locations.

Analysis of perfluorochemical concentrations in water—algae–zebra mussels–round gobies–smallmouth bass—can provide information on the food-chain transfer of these compounds to higher trophic-level organisms. Zebra mussels can sequester contaminants by ingesting algae and other suspended materials, or directly from water (Bruner *et al.* 1994). Round gobies generally eat zebra mussels ranging in size from 3 to 12 mm (Jude *et al.* 1995). In particular, small round gobies (< 50 mm standard length) feed primarily on benthic arthropods such as amphipods, whereas the diet of larger gobies is composed primarily of zebra mussels. In addition, crayfish have been found to consume zebra mussels in laboratory studies (Martin and Corkum 1994). Round gobies are prey species for several game fish species, including smallmouth bass and brown trout (*Salmo trutta*). Smallmouth bass from Calumet Harbor, the St. Clair River, and western Lake Erie have been shown to prey on round gobies (Savitz *et al.* 1996).

In addition to the benthic invertebrates and forage fish species, tissues of Chinook salmon (*Oncorhynchus tshawytscha*), lake whitefish (*Coregonus clupeaformis*), brown trout, carp (*Cyprinus carpio*), green frogs (*Rana clamitans*), snapping turtles (*Chelydra serpentina*), bald eagles (*Haliaeetus leucocephalus*), and mink (*Mustela vison*) collected from various locations in Michigan were also analyzed for determination of the concentrations of perfluorinated compounds in higher trophic-level organisms of the Great Lakes food chain. Mink are carnivores and primarily feed on small mammals, birds, frogs, crayfish, fish, lizards, small snakes, and insects. The bald eagle's diet consists of fish, turtles, waterbirds such as ducks, small mammals such as muskrats, and snakes. Snapping turtles eat algae, aquatic insects, small fish, frogs, snails, and young waterfowl.

Materials and Methods

Sampling

Biotic samples were collected from several rivers in Michigan and in the Calumet River in Indiana, USA, during 1998–2001. The sampling locations are shown in Figure 1. Benthic algae, amphipods, zebra mussels, crayfish, round gobies, and smallmouth bass were collected from various locations within 1 km of the Raisin River mouth to Lake Erie, and from the St. Clair River at its confluence with the Belle River, at Marine City, and at Algonac, Michigan. The benthic organisms were also collected from the Calumet River at its confluence with Lake Michigan in Indiana. All of the biotic samples were collected during July to November, 1998 and 1999. Water samples were collected from the St. Clair and Raisin Rivers in 2001 at the locations where benthic organisms had been collected. No water samples were collected from the Calumet River.

Several hundred zebra mussels were collected from rocky substrata at each location by snorkeling or scuba diving. Fishes were collected by seining or by electroshocking. Amphipods were collected by turning over rocks and using forceps to collect individual organisms. Benthic algae were collected by scraping hard surfaces with a clean toothbrush (for nonfilamentous forms), or by hand-picking tufts of filamentous algae. Skinless fillets were analyzed for smallmouth bass, whereas the whole body was analyzed for round gobies. Soft tissues of zebra mussels were analyzed. Tissues from several individuals per species (including fish) were pooled to obtain an adequate mass for extraction. Length of each individual fish was measured immediately after collection, and individuals were pooled on the basis of sizes for analysis (Table 1).

A few higher trophic-level fishes such as Chinook salmon, lake whitefish, brown trout, and carp were also collected from Michigan waters in 1999 and 2000. Liver and egg samples were obtained from these fishes for analysis. Muscle tissue was analyzed for carp. Plasma from snapping turtles collected from Macomb County, along Lake St. Clair, in June 1999, was analyzed. All of the turtles were adults. A large mass of eggs was found in all female turtles. Livers from adult green frogs collected in 1998 from the vicinity of Calkins Dam on the Kalamazoo River in southwestern Michigan were analyzed. Livers were analyzed from mink collected by trappers from the Kalamazoo River watershed in 2000–2001.

Carcasses of bald eagles that were found dead in the Upper Peninsula of Michigan in 2000 were collected by or submitted to Rose Lake Wildlife Research Center, Lansing, Michigan. The carcasses were transported to the wildlife research center and, upon receipt, they were necropsied and the cause of death was determined. Samples of liver, muscle, fat, kidney, and gallbladder (from nondecomposed carcasses) were wrapped in solvent-cleaned aluminum foil and stored at −20°C until analysis. The gallbladder was filled with bile when collected.

Chemical Analysis

Tissue samples of fish, mussel, amphipods, and algae were analyzed by a solid-phase extraction (SPE) method. Approximately 1 g of sample was cut into small pieces, and 5 mL of Milli-Q water was added. Samples were then ground using an Ultra-Turrax tissue homogenizer. To 1 mL of the extract taken in a polypropylene tube, 5 mL of acetonitrile was added; the tube was shaken for 20 min. The homogenate was then centrifuged at 2000 rpm for 10 min. The supernatant (acetonitrile layer) was decanted into a polypropylene tube containing 40 mL of Milli-Q water. PFOS, PFOSA, PFOA, and PFHS were extracted from the samples using C18 SPE extraction cartridges (1 g, Sep-Pak 6 cc tri-functional C_{18}; Waters, Milford, MA). Sample flow rate was maintained at 5–7 mL/min. SPE cartridges were conditioned by washing twice with approximately 5 mL of methanol, followed by approximately two 5-mL aliquots of water; care was taken not to allow the column to run to dryness after each wash. After conditioning, samples were passed through the cartridge, which was then allowed to dry. Cartridges were then eluted with 0.5 mL methanol.

Bald eagle liver, kidney, muscle, testes, ovaries, and gallbladder were analyzed using an ion-pair extraction method described elsewhere (Hansen *et al.* 2001; Kannan *et al.* 2001a). Similarly, livers and eggs of Chinook salmon and lake whitefish, muscle tissue of carp, eggs of brown trout, livers of frog and mink, and plasma of snapping

Table 1. Concentrations of PFOS, PFOSA, PFOA, and PFHS in water (ng/L) and benthic organisms (ng/g, wet weight) of a Great Lakes food chain

Location	Species/specimen	PFOS	PFOSA	PFOA	PFHS	Remarks (size, date)
Raisin River	Water (ng/L)	3.5	<10	14.7	<1	Near Monroe, Mar 2001
	Benthic algae	2.4	<1	<0.2	<2	Near Ford Plant, Sept 99
	Amphipods	2.9	<2	<5	<1	Near Ford Plant, Sept 99
	Zebra mussel	3.1	2.7	<5	<1	8–20 mm, Oct 98
		<2	3.8	<5	<1	10–19 mm, Aug 99
	Crayfish	4.3	1.6	<0.2	<2	Sep 99, 61–66 mm
	Round gobies	11.2	1.6	<0.2	<2	Near Edison, 70–96 mm, Sept 99
		7.2	2.1	<2	<1	77–87 mm, Oct 98
		6.6	1.8	<0.2	<2	Port of Monroe, 95–109 mm, Oct 98
	Smallmouth bass	41.3	2.7	<2	<1	56–98 mm, Sept 98
		2.0	1.2	<2	<1	69–146 mm, Sept 99
		3.6	1.4	<2	<1	174–210 mm, Sept 98
		5.8	1.8	<2	<1	250–257 mm, Sept 99
		7.6	2.4	<2	<1	256–314 mm, Sept 98
		19.8	4.1	<2	<1	343–406 mm, Sept 98
		8.6	1.2	<2	<1	349–357 mm, Sept 99
		17.8	<1	<2	<1	414–416 mm, Sept 99
St. Clair River	Water (ng/L) (n = 3)	2.6 (1.9–3.9)	<10	4.4 (4.0–5.0)	<1	Apr 2001
	Benthic algae	2.6	<1	<0.2	<2	Marine City, July 99
	Amphipods	<2	<2	<5	<1	Marine City, Sept 99
	Zebra mussel	<2	<2	<5	<1	Marine City, 12–24 mm, Nov 98
	Crayfish	2.4	1.4	<0.2	<2	Marine City, 40–75 mm, Sept 99
	Round gobies	19.1	3.4	<0.2	<2	Marine City, 77–82 mm, July 99
		7.7	1	<0.2	<2	Belle River, 77–83 mm, Sept 98
		9.6	1.8	<0.2	<2	Marine City, 82–102 mm, July 99
		14.9	1.8	<0.2	<2	Belle River, 88–102 mm, Sept 98
		8.9	1.9	<0.2	<2	Belle River, 112–120 mm, Sept 98
		21.5	5.2	<0.2	<2	St.Clair River, 122–140 mm, Sept 99
		8.7	<1	<0.2	<2	Marine City, 128–133 mm, July 99
		7.7	1.1	<0.2	<2	Belle River, 159 mm, Sept 98
	Smallmouth bass	<2	6.3	<2	<1	174–203 mm, Aug 99
		2.7	1.1	<2	<1	312–368 mm, Oct 98
Calumet River						
	Benthic algae	3.1	<1	<0.2	<2	Calumet Harbor, July 99
	Amphipods	<2	<2	<5	<1	Calumet Harbor, July 99
	Zebra mussel	<2	<2	<5	<1	5–23 mm, Sept 98
		<2	<2	<5	<1	8–21 mm, Sept 98
		<2	<2	<5	<1	10–21 mm, July 99
	Crayfish	3.7	<1	<0.2	<2	Calumet Harbor, 81–100 mm, July 99
	Round gobies	4.1	<1	<0.2	<2	Calumet Harbor, 77–92 mm, July 99
	Smallmouth bass	5.1	<1	<0.2	<2	Calumet park, 256–314 mm, May 98
		7.6	<1	<2	<1	Calumet Harbor, 335–355 mm, Aug 99
		2.5	<1	<2	<1	380–390 mm, May 98
		2.6	<1	<2	<1	415–425 mm, May 98

PFOS = perfluorooctanesulfonate; PFOSA = perfluorooctane sulfonamide; PFOA = perfluorooctanoate; PFHS = perfluorohexanesulfonate.

turtles were analyzed by the ion-pair extraction method. Briefly, homogenates of the tissue matrices were prepared in 5 mL of water. One milliliter of 0.5 M tetrabutylammonium hydrogen sulfate solution and 2 mL of sodium carbonate buffer (0.25 M, pH 10) were added to 1 mL of plasma or tissue homogenate in a polypropylene tube, and the tube was thoroughly mixed for extraction. Five milliliters of methyl-*tert*-butyl ether (MTBE) was added to the above mixture and shaken for 20 min. After centrifugation, the MTBE layer was transferred into another polypropylene tube. The solvent was evaporated under nitrogen and replaced with 1 mL of methanol. This extract was passed through a nylon mesh filter (0.2 μm) into an HPLC vial.

Water samples were analyzed following the SPE method described elsewhere (Yamashita *et al.* 2004). Water samples were allowed to settle, and particulate matter was kept to a minimum for extraction. Briefly, a sample aliquot of water (100 mL) was passed through the preconditioned Oasis® HLB (60 mg, 3 cc) cartridges (Waters Corporation, Milford, MA) at a rate of 1 drop/sec. The cartridges were not allowed to dry out prior to passing water samples. The cartridges were then washed with 1 mL of 40% methanol in water, which was discarded. The target analytes were eluted with 5 mL of methanol, and were collected in a polypropylene tube. The solvent was evaporated under a gentle stream of pure nitrogen to 1 mL for HPLC-MS/MS analysis. Particles that appeared in the final solution of a few of the water samples were removed by filtration using a nylon syringe filter.

Quantitative analyses were performed by monitoring a single product ion selected from a primary ion characteristic of a particular fluorochemical using HPLC-ES/MS/MS. For example, molecular ion m/z = 499, selected as the primary ion for PFOS ($C_8F_{17}SO_3^-$) anal-

ysis, was fragmented further to produce ion m/z = 99 (FSO_3^-). The characteristic product ion (m/z = 99) was monitored for quantitative analysis. Quantitation of the target analytes was based on quadratic regression fit analysis weighted 1/x of a single unextracted curve for each group of tissue samples. High or low points on the curve were deactivated, if necessary, to provide a better linear fit over the curve range most appropriate to samples. Low points on the curve with peak areas less than that of the average response from the procedural blanks were deactivated, to disqualify a data range that may have been significantly affected by background levels of the analyte. Quantitation of each analyte was based on the response of one specific product ion using the multiple reaction-monitoring (MRM) mode of the instrument. Unextracted calibration standards were prepared at approximately 0.10 ng/mL–750 ng/mL for analysis. The coefficient of determination (r^2) of each standard curve was >0.99.

Specificity for analyte identification was demonstrated by chromatographic retention time and mass spectral daughter ion characterization. Additional confirmatory tests were performed for PFOS. In the electrospray tandem mass spectrometry (ES/MS/MS) system, the 499 Da –> 80 Da transition can provide a stronger signal than the 499 Da –> 99 Da transition of the PFOS analysis. However, in the analysis of tissue samples collected from some species, an unidentified interferent may be present in the 499 Da –> 80 Da transition. Although this interferent is rarely observed, quantitation was based on the 499 Da –> 99 Da transition to ensure complete selectivity. To confirm the identity of PFOS in samples containing >70 ng/g (>10 ng/mL), at least two transitions were monitored and were required to show quantitative agreement to within ±30%. Typically, 499 > 99 and 499 > 80 transitions were monitored. On the occasions when these two transitions differed by more than 30%, the sample was reanalyzed by monitoring for the 499 > 80, 499 > 99, and 499 > 130 transitions. If the 499 > 130 and 499 > 99 transitions showed quantitative agreement to within ±30%, the PFOS concentration was considered confirmed.

A well-characterized matrix of rabbit liver was used as surrogate tissue for matrix blanks. All water blank peak areas were less than or equal to half the peak area of the limit of quantitation (LOQ) for the compounds of interest. The LOQ is equal to the lowest acceptable standard in the calibration curve (defined as a standard within ±30% of the theoretical value), and has a peak area two times greater than the analyte peak area detected in the average of the water blanks. Because low levels of the target analytes are ubiquitous in the laboratory, it is imperative that these criteria for LOQ determination be observed. The LOQs for perfluorinated compounds in biological matrices analyzed using the SPE method ranged from 1 to 10 ng/g, wet wt. The LOQs for the samples analyzed using the ion-pair extraction method ranged from 7.5 to 75 ng/g, wet wt. Fluoropolymer-containing vial caps and sample containers were avoided.

Several matrix spikes were prepared for tissue samples. These tissues were spiked with target compounds at levels of 1, 1.4, 3, 4, 10, and 14 ng/g for amphipod, zebra mussel, benthic algae, crayfish, round gobies, and smallmouth bass muscle, respectively, and were passed through the whole analytical procedure. Mink livers were spiked at 600 ng/g level. Recoveries of PFOS ranged from 67% in benthic algae to 136% in bass muscle. Recoveries of PFHS varied from 65% to 140%. Recoveries of PFOSA and PFOA were less than 50% in most cases and varied widely. Therefore, the reported values for PFOSA and PFOA are considered semiquantitative. The reported concentrations were not corrected for recoveries. The measurement of accuracy available at this time, matrix spike studies, indicates that the data for water, benthic algae, amphipods, zebra mussel, crayfish, round gobies, and smallmouth bass are within ±50% for PFOS and PFHS. PFOS data for Chinook salmon, lake whitefish, brown trout, carp, snapping turtle, frog, mink, and bald eagle tissues should be considered accurate within ±30%. Because of the variations in recoveries and accuracy of PFOS analysis, a biomagnification factor (BMF) of 2 or less should be considered insignificant.

Results and Discussion

PFOS was the most commonly detected fluoroorganic compound in various organisms of the Great Lakes food chain examined (Table 1). PFOS and PFOA were found in water samples from all of the locations, at mean concentrations of 2.6–17 and 4.4–22 ng/L, respectively. Concentrations of PFOS in water samples were within the range of <0.8–30 ng/L, reported for several Michigan surface waters (Sinclair *et al.* 2004). Concentrations of PFOA were slightly higher than those of PFOS in water samples. The measured concentrations of PFOS and PFOA were similar to those reported for inland and coastal waters of Japan (Taniyasu *et al.* 2003; Saito *et al.* 2003), but severalfold lower than those reported for areas impacted by local sources of contamination (Schultz *et al.* 2004; Hansen *et al.* 2002; Moody *et al.* 2002).

Concentrations of PFOS in lower trophic-level organisms in the food chain are on the order of a few nanograms per gram (ppb). This is approximately three orders of magnitude greater than the concentrations found in surface waters. For example, the concentration of PFOS in a water sample from the Raisin River was 3.5 ng/L, whereas that in benthic algae, amphipods, and zebra mussels was in the range of 2.4–3.1 ng/g, wet weight. This suggests a bioconcentration factor (BCF) of PFOS of approximately 1000. Based on the water concentration of 3.5 ng/L and a whole-body PFOS concentration in round gobies of 8.3 ng/g, wet weight, a BCF of 2400 was calculated. This value is within the range reported for lake trout exposed to PFOS under laboratory conditions (Martin *et al.* 2003). BCFs of PFOS were reported to be 1100 in carcass and 5400 in liver of rainbow trout exposed under laboratory conditions (Martin *et al.* 2003). Despite the occurrence of PFOA in water samples, this compound was not found in the tissues of any of the benthic organisms analyzed at a LOQ of 0.2–2 ng/g. This may be due to a low bioconcentration potential of PFOA. The BCF reported for PFOA in rainbow trout exposed under laboratory conditions ranged between 4 and 27; this range is 1000-fold lower than that reported for PFOS (Martin *et al.* 2003).

In general, concentrations of perfluorinated compounds were low in lower trophic-level organisms such as amphipods and zebra mussels (e.g., <2–4.3 ng/g, wet weight) and relatively higher in round gobies and smallmouth bass (e.g., 2–41.3 ng/g, wet weight). Mean concentrations of PFOS in round gobies and smallmouth bass from the Raisin River were 8.3 and 13.3 ng/g, wet weight, respectively. The concentrations of PFOS in round gobies and smallmouth bass were two- to fourfold higher than those found in benthic algae and crayfish, suggesting a BMF of two to four between algae/crayfish and round gobies. However, no marked variation was noted for the concentrations of PFOS among the three benthic organisms analyzed; algae, amphipods, and zebra mussels. Similarly, concentrations of PFOS were not significantly different among the three locations investigated. No size-related differences in the concentrations of PFOS in round gobies or smallmouth bass could be discerned. The mean concentration of PFOS in round gobies from the St. Clair River was 12.3 ng/g, wet weight, which was greater than the concentrations found in smallmouth bass collected from the same location. Similarly, concentrations of PFOS in round gobies and in small-

Table 2. Concentrations of PFOS, PFOSA, PFOA, and PFHS (ng/g, wet wt) in fish from Michigan waters, USA

Species	Tissue	Location	PFOS	PFOSA	PFOA	PFHS
Chinook salmon (n = 6)	Liver	Webber Dam, Grand River	100 (32–173)	<19	<72	<17
Lake whitefish (n = 5)	Liver	Thunder Bay, Lake Huron	67 (33–81)	<19	<72	<17
Lake whitefish (n = 2)	Eggs	Thunder Bay, Lake Huron	263 (145–381)	<19	<36	<34
Brown trout (n = 3)	Eggs	Marquette, Lake Superior	64 (49–75)	<19	<18	<34
Carp (n = 10)	Muscle	Saginaw Bay	124 (59–297)	<19	<36	<34

Notes: Values below LOQ are denoted by '<'; Values below the detection limit were not included in the estimation of mean (in parentheses). For abbreviation, see Table 1.

Table 3. Concentrations of PFOS, PFOSA, PFOA, and PFHS (ng/g, wet wt) in livers of mink and green frog collected from Kalamazoo, and in plasma (ng/mL) of snapping turtles from Macomb County, Michigan

Sample	PFOS	PFOSA	PFOA	PFHS	Remarks (sex, location, age, weight)
Mink (n = 7)	18000 (1280–59,500)	103 (<2–181)	<2–3.33*	21 (7.5–40)	Male, Kalamazoo River watershed, age 0.5–3 yrs, 0.7–1.1 kg
Mink (n = 1)	41	<2	12.2	6.3	Female, Kalamazoo River watershed
Green frog (n = 2)	168 (50–285)	<19	<72	<6	Adult, Calkin's dam
Green frog (n = 2)	<35	<19	<72	<6	Adult, 118th pond and Swan Creek
Snapping turtle (n = 2)	137 (105–169)	<1–15.5[a]	<2.5	<1	Adult male, 8.9–9.2 kg
Snapping turtle (n = 3)	6.13 (<1–8.8)	<1	<2.5	<1	Adult female, 3.2–5.8 kg

Note: Values below the detection limit were not included in the means (in parentheses).
[a] Only one detectable observation.
For abbreviation, see Table 1.

mouth bass were similar (4.1 and 4.5 ng/g, wet weight, respectively) in samples collected from the Calumet River. The apparent lack of biomagnification of PFOS from round goby to smallmouth bass could be due to the fact that the whole body was analyzed for round gobies, whereas only muscle tissue was analyzed for smallmouth bass. Therefore, the comparison of PFOS concentrations between these two species is not direct. Because PFOS binds to proteins (rather than lipids) and accumulates in liver and blood, a whole-body analysis would be needed to estimate biomagnification potential in higher trophic-level organisms. However, analysis of whole body would be a daunting task for large animals such as salmonid fishes, mink, and predatory birds.

Because perfluorinated compounds preferentially accumulate in livers, this tissue was analyzed from Chinook salmon and lake whitefish collected from Michigan waters. The concentrations of PFOS in livers of these predatory fish were compared with those of prey species such as zebra mussels, round gobies, and amphipods (Table 2). Livers of Chinook salmon collected from the Grand River contained an average PFOS concentration of 100 ng/g, wet weight, a level approximately 10- to 20-fold greater than that found for round gobies. The mean concentration of PFOS in livers of lake whitefish (67 ng/g, wet weight) collected from Thunder Bay, Lake Huron was 6- to 8-fold greater than that found for round gobies, and 10- to 20-fold greater than those found in zebra mussels and amphipods. The diet of lake whitefish includes zebra mussels and insect larvae, whereas the diet of Chinook salmon includes small fishes such as minnows, alewife, and smelt (Rybicki and Clapp 1996). Carp from Saginaw Bay contained concentrations of PFOS as great as 297 ng/g, wet weight, in muscle tissue (Table 2). Carp feed primarily on zebra mussels and trout eggs (Marsden 1997). Also, relatively high concentrations of PFOS were found in the eggs of fish (Table 2). Concentrations in eggs were higher than those found in the livers of lake whitefish. This suggests preferential binding of PFOS to egg albumin, and transfer of this compound to the eggs. Thus, in oviparous organisms, females may excrete considerable burdens of perfluorinated compounds via egg laying. Early life stages of organisms are vulnerable to the effects of chemical exposures. Occurrence of great concentrations of PFOS in eggs suggests exposure of the young developing from these eggs. Great concentrations of PFOS have been reported to occur in the eggs of fish-eating water birds (Giesy and Kannan 2001; Rattner *et al.* 2004).

It is also worth that PFOSA was found in several lower trophic-level organisms including zebra mussel and round gobies. However, PFOSA was not found in the livers of higher trophic-level fish such as Chinook salmon. PFOSA is an intermediate metabolite during the transformation of precursor molecules such as n-ethyl perfluorooctanesulfonamidoethanol or n-methyl perfluorooctanesulfonamidoethanol, which are used as surfactants in a variety of products. Transformation of n-ethyl perfluorooctanesulfonamide to PFOS and PFOSA by rainbow trout microsomes has been reported (Tomy *et al.* 2004).

High concentrations of PFOS were found in the livers of mink collected from the Kalamazoo River watershed (Table 3). A concentration of 59,500 ng/g, wet weight, was found in the liver of an adult male mink. This is the highest concentration reported for PFOS in any aquatic organism studied thus far. Concentrations of PFOS in mink from the Kalamazoo River watershed were 10 to 20 times greater than those in the livers of mink from Illinois and Massachusetts, USA (Kannan *et al.* 2002c). The mean concentration of PFOS in liver from male mink was 18,000 ng/g, wet weight. This

Table 4. Concentrations of PFOS, PFOSA, PFOA, and PFHS (ng/g, wet wt) in various tissues of bald eagles collected from Upper Peninsula of Michigan in 2000, USA

Eagle no.	Tissue	PFOS	PFOSA	PFOA	PFHS	Remarks (sex, location, cause of death)
Bald eagle 1 (373)	Liver	1740	<75	<19	<19	Adult male, Cecil Bay, died of bacterial infection
	Kidney	1480	<75	<38	<19	
	Gall bladder	1490	<75	<38	<19	
	Muscle	96.2	<75	<38	<19	
Bald eagle 2 (374)	Liver	394	<75	<19	<19	Adult male, Ironwood, died of trauma
	Testes	183	<75	<38	<19	
Bald eagle 3 (377)	Muscle	79.3	<75	<38	<19	Juvenile female, Mackinac, peritonitis
	Kidney	446	<75	<38	<19	
Bald eagle 4 (378)	Muscle	<7.5	<75	<38	<19	Juvenile female, Menominee County, trauma
	Liver	75.4	<75	<19	<19	
	Kidney	74.6	<75	<38	<19	
	Ovary	68.0	<75	<38	<19	
Bald eagle 5 (379)	Muscle	13.9	<75	<38	<19	Adult female, Paint River, trauma
	Liver	79.1	<75	<19	<19	
Bald eagle 6 (381)	Muscle	<7.5	<75	<38	<19	Adult male, Fence River, trauma
	Liver	26.5	<38	<38	<38	
	Kidney	35	<75	<38	<19	
Bald eagle 7 (382)	Muscle	<7.5	<75	<38	<19	Juvenile female, Kallio, trauma
	Liver	47.2	<38	<19	<38	

For abbreviation, see Table 1.

value is 100 times greater than those measured in fish or other aquatic benthic organisms analyzed. Prey items of mink include small mammals such as shrews, muskrats, fish (such as crayfish, carp, smallmouth bass), and turtles. PFOSA, PFOA, and PFHS were also found in the livers of mink. However, concentrations of these compounds were two to three orders of magnitude less than the concentrations of PFOS. Water samples collected from several locations in the Kalamazoo River also contained PFOS concentrations 5- to 10-fold greater than those from the Raisin and St. Clair Rivers in Michigan (Sinclair *et al.* 2004). Concentrations of PFOS in livers of mink were 1×10^6 fold greater than the concentrations measured from water from the Kalazamoo River (17 ng/L, Sinclair *et al.* 2004). A PFOS concentration as high as 285 ng/g, wet weight, was found in the livers of frogs collected from the Kalamazoo River. The occurrence of high concentrations of PFOS in mink from the Kalamazoo River suggests the presence of local sources of this compound.

Blood plasma of snapping turtles collected from Macomb County near Lake St. Clair contained considerable concentrations of PFOS (Table 3). PFOS concentrations ranging from 105 to 169 ng/mL (mean: 137 ng/mL) in males and from <1 to 8.8 ng/mL (mean: 6.13 ng/mL) in females were found. This considerable gender difference in the concentrations of PFOS in snapping turtles suggests oviparous transfer of PFOS via egg laying, similar to that observed for fish. As mentioned earlier, all of the female turtles collected in the study were adults, and necropsy revealed the presence of large mass of eggs.

PFOS was also found in the tissues of bald eagles collected from the Upper Peninsula of Michigan (Table 4). Occurrence of PFOS in ovaries, testes, kidneys, and muscle suggests perfusion of this compound in various body tissues. Earlier studies reported the occurrence of PFOS in brain tissues of laboratory-exposed rats (Austin *et al.* 2003). In bald eagles, liver contained the greatest concentration of PFOS, although concentrations in kidneys were almost as high as those found in the livers. The highest concentration of PFOS, 1740 ng/g, wet weight, in the liver of an adult male bald eagle was approximately 10- to 20-fold greater than those found in the livers of Chinook salmon or muscle of carp analyzed in this study. The mean concentration of PFOS in the livers of bald eagles was 400 ng/g, wet weight, which is four- to fivefold greater than the concentrations found in several higher trophic-level fish analyzed in this study. In addition to livers, blood plasma from nestling bald eagles also contained great concentrations of PFOS (Kannan *et al.* 2001a). A PFOS concentration as high as 2220 ng/mL has been reported in the plasma of bald eagles from Wisconsin, USA (Kannan *et al.* 2001a). A sample of gallbladder of an adult male bald eagle also contained a PFOS concentration similar to that found in the liver. PFOS has been reported to accumulate in gallbladder, similarly to bile salts, and to undergo enterohepatic circulation (Johnson *et al.* 1984), due to its structural similarity to bile acids containing both lipophilic and hydrophilic regions.

Assuming that PFOS concentrations measured in gallbladder reflect the concentrations in bile, biliary excretion of PFOS can be estimated. The biliary excretion rate can be calculated as:

$$\text{Biliary excretion rate (\% per day)} = [\text{Amount in bile}(\mu g) \div \text{Amount in body}(\mu g)] * 100$$

For this estimation, data for muscle, liver, and gallbladder from a single individual were used (no. 373; Table 4). The excretion rate was calculated on the basis of the amount (burden) of PFOS in liver, kidney, muscle, and blood, and the amount (burden) in bile/gallbladder. The body weight of the eagle was 3.5 kg. It was assumed that liver, kidney, and blood account for 4% each of the total body mass and that muscle tissue accounts for 30% of the body mass. The PFOS con-

centration in blood was assumed to be similar to that in the liver. Daily bile excretion was assumed to be 10 g. Based on the concentrations of PFOS found in liver, kidney, blood, and muscle, the total body burden of PFOS in this eagle was estimated to be 800 μg. The burden of PFOS in bile was 14.9 μg. Based on these figures, the excretion rate of PFOS was estimated to be 1.9% per day, which is approximately two to three orders of magnitude greater than the rates estimated for persistent organochlorine pollutants such as PCBs and DDT (Senthilkumar *et al.* 2002). This result may suggest that PFOS is excreted relatively rapidly from the body. However, unlike persistent organochlorine pollutants, binding of perfluorinated compounds to proteins and retention by enterohepatic circulation are the major factors that determine accumulation and retention in biota.

In summary, these results suggest the occurrence of PFOS in lower trophic-level benthic invertebrates of a Great Lakes food chain. Concentrations of PFOS in benthic invertebrates and also in round gobies were 1000-fold greater than those in surrounding water. PFOS tends to biomagnify in higher trophic-level fish such as salmonids. A BMF of 10–20 was determined between round gobies and Chinook salmon liver. Concentrations of PFOS were the greatest in mink and bald eagles. A BMF of 5–10 was observed between salmon liver and eagle/mink livers. Based on the fact that higher trophic-level organisms have greater capacity to metabolize environmental contaminants than do lower trophic-level organisms, precursor compounds (e.g., n-ethyl/n-methyl perfluorooctanesulfonamidoethanol) of PFOS that are present in lower trophic-level organisms as unmetabolized or partially metabolized molecules serve as a contributory source of PFOS for higher trophic-level organisms. This may be a source of error in the estimation of BMF in this study. Further studies are needed to evaluate the occurrence and metabolism of precursor compounds of PFOS and other related fluorinated compounds in aquatic organisms.

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Issue Paper 2

Exposure and Toxicity of Perfluorochemicals

By Dr. Richard DeGrandcamp

Perfluorochemicals (PFCs) are a large family of related manmade chemicals that share similar chemical properties and produce similar toxic effects. PFCs do not occur naturally in the environment. Over the last 50 years, PFCs have been synthesized in massive quantities and used in numerous commercial products, although manufacturing of some PFCs has been voluntarily discontinued. All PFCs share a basic chemical structure consisting of a linear carbon chain of varying lengths to which fluorine is bound with a functional reactive end group. The carbon-fluorine bond is considered the strongest chemical bond in organic chemistry, which makes PFCs virtually indestructible. Although the length of the carbon chain largely determines the chemical properties of each PFC compound, the reactive end group governs the inherent toxicity. Within the family of PFCs, there are groups of perfluoroalkyl acids, amides, and alcohols, which are either byproducts, end products, or processing compounds used in the synthesis of fluoropolymers.

In addition to PFCs, there is another type of perfluorocarbons called perfluorochemical telomers (PTCs). The importance of this group is two fold. Although they have been studied less than have PFCs, environmental exposures to PTCs may also pose risks to human health. Secondly, there are indications that PTCs degrade to form PFCs. For example, the 8-2 telomer, heptadecafluoro-1-decanol, can metabolize or degrade to perfluorooctanoic acid (PFOA; Dinglasan *et al*. 2004). Unfortunately, it has become common practice to limit laboratory analysis only to PFCs, despite studies that show PTCs are also present. This could result in underestimating the toxic potential of some contaminated media. Uncontrolled environmental releases of PFCs always occur as complex mixtures. Therefore, it is necessary to analyze for and consider the toxicity and risk associated with exposure to all perfluorinated compounds because people exposed to contaminated soils and groundwater will be simultaneously exposed to all contaminants.

High ubiquitous anthropogenic backgrounds level of PFCs have been found throughout the United States (U.S.). These high levels are the result of point source discharges into the environment, manufacturing processes, and use of commercial products containing PFCs for more than 50 years. They have been detected in a variety of environmental media around the globe in surface and ground water, air, sludge,

soils, sediments, plants and animals, and have even been detected in the polar ice caps. Once released into the environment, PFCs persist for tens of decades because they are highly resistant to all normal processes of degradation that occur in the environment (i.e., photoxidation, direct photolysis, and microbial or hydrolytic degradation). The half-life of most PFCs (the time required for one-half the concentration to decrease) can be more than 50 years, and complete degradation can take more than a century. The other important physical characteristic of PFCs is their mobility in surface and ground water. PFCs have been detected far downstream from the initial release.

PFOA and perfluorooctane sulfonic acid (PFOS) have been measured in outdoor urban air samples at concentrations up to 46 and 919 pg/cubic meters, respectively. PFOA, PFOS, and perfluorohexane sulfonic acid (PFHxS) have been detected in indoor dust samples at concentrations up to 3,700; 5,065; and 4,305 ng/g, respectively. The ubiquitous releases into the environment across the U.S. are reflected in the high body burden levels as measured in blood serum in the general U.S. population. Serum levels of PFCs (particularly PFOA and PFOS) have consistently been detected in the blood of most Americans at alarmingly high levels. The Center of Disease Control and Prevention (CDC) first started including PFC analysis as part of its biomonitoring program and reporting the levels in its "National Report on Human Exposure to Environmental Chemicals "starting in 1999. Of the 12 different PFC compounds that CDC measured in blood serum of the general U.S. population, PFOS, PFOA, PFHxS, and perfluorononanoic acid (PFNA) have been consistently detected in nearly every sample. Table 1 shows the serum PFC levels in the general population reported in the latest CDC report (represents levels measured in 2003-2004; CDC 2009).

Table 1. PFC Serum Concentrations in U.S. Population CDC Fourth National Report on Human Exposure to Environmental Chemicals

PFC Compound	50th Percentile Concentration	95th Percentile Concentration
Perfluorobutane Sulfonic Acid (PFBuS)	< LOD	< LOD
Perfluorodecanoic Acid (PFDeA)	< LOD	.0.9
Perfluorododecanoic Acid (PFDoA)	< LOD	< LOD
Perfluoroheptanoic Acid (PFHpA)	< LOD	0.40

Perfluorohexane Sulfonic Acid (PFHxS)	1.93	8.30
Perfluorononanoic Acid (PFNA)	1.0	3.20
Perfluorooctanoic Acid (PFOA)	4.10	9.80
Perfluorooctane Sulfonic Acid (PFOS)	21.2	54.60
Perfluorooctane Sulfonamide (PFOSA)	< LOD	0.30
2-(N-Ethyl-Perfluorooctane sulfonamido) Acetic Acid (Et-PFOSA-AcOH)	< LOD	< LOD
2-(N-Methyl-perfluorooctane sulfonamido) Acetic Acid (Me-PFOSA-AcOH)	< LOD	1.30
Perfluoroundecanoic Acid (PFUA)	< LOD	0.60

LOD: Limit of Detection
Concentration is µg/L (ppb) in serum.
Measurements represent burden levels for 2094 people representing the general U.S. population.

Other studies have reported similar levels in smaller populations (Calafat *et al.* 2007a, 2007b; Olsen *et al.* 2003a, 2005). Analysis of different genders and age groups show males have higher levels of PFOA and PFOS than do females, and there is a slight increase in levels of PFOS with age (Calafat *et al.* 2007a; Harada *et al.* 2004; Olsen *et al.* 2003*a*). In a study of 598 blood donors aged 20 to 69, Olsen *et al.* (2003a) noted surprisingly little variance across five widely dispersed U.S. cities, which means that exposures in the general U.S. population are relatively uniform. It is important to note that PFOS and PFOA are always highly correlated in each blood sample, meaning that exposure to these two compounds occurs simultaneously.

Although CDC did not start monitoring PFC body burdens until 1999, smaller studies conducted earlier showed that serum PFC concentrations increased dramatically from 1974 to 1989 (Olsen *et al.* 2005). During this period, levels of PFOS, PFOA, and Et-PFOSA-AcOH increased, 25%, 162%, and 204% respectively. Serum levels of PFCs, particularly PFOS, appear to be about two to three times higher in the U.S. than in some other industrialized countries such as Columbia, Brazil, Poland, Belgium, Malaysia, Korea, and Japan; about eight- to 16-fold higher than in Italy and India (Kannan *et al.* 2004); and more than 30-fold higher than in Peru (Calafat *et al.* 2006b).

Bioaccumulation in animals is the difference between the rate of intake (primarily ingestion) and elimination (primarily in urine). Studies have shown that PFCs are well absorbed orally, but only slowly eliminated in humans. Although the human body is very effective in detoxifying and eliminating most chemicals, PFCs resist the normal metabolic processes that convert toxic chemicals to less harmful compounds. As a result, PFCs circulate in the blood for decades after ingestion and are only eliminated, largely unchanged, after decades (Johnson *et al.* 1984; Kemper and Nabb 2005; Kuslikis *et al.* 1992; Ophaug and Singer 1980; Vanden Heuvel *et al.* 1991). Bioaccumulation can lead to build up of PFCs to extremely high concentrations, even when the levels detected in soil and groundwater that are the source of exposure are at fairly low levels. For example, some fish bioconcentrate PFOS greater than 2,000-fold over the levels measured in the water in their aquatic environments, and this has resulted in dramatic accumulations in different animal species over time. For example, PFOS and PFOA levels in archived bird eggs from Sweden increased 30-fold from 1968 to 2003 (Holmstrom *et al.* 2004). In humans, the serum:drinking water bioaccumulation factor for PFOA (the PFC studied the most) has been shown to be approximately 140. A person consuming drinking water contaminated with 1 ppb PFOA will have a blood serum level of about 140 parts per billion (ppb).

After people ingest PFCs, they are rapidly absorbed into the blood circulation where they bind very strongly to proteins. PFCs are only very slowly eliminated from the body, and it can be decades before even a small ingested amount is eliminated. The time required to eliminate chemicals from the body is conventionally represented as the "half-life." This is defined as the time necessary for one-half the body burden to be reduced by one-half. The half-life is a very important toxicological concept because the longer a chemical circulates in the blood, the greater potential for cellular and organ damage. The half-life for PFOA is estimated to be about four years, and it is approximately five to seven years for PFOS (Olsen *et al.* 2007a). It typically takes about seven half lives to completely eliminate a chemical from the body once it is absorbed into the circulation. Accordingly, a person ingesting PFOA or PFOS today will not completely eliminate them from their bodies for 28 and 63 years, respectively. In general, PFC compounds with shorter carbon chain lengths are eliminated from the body faster than longer and heavier PFC compounds.

In contrast to the very slow rate of elimination in humans, PFCs are rapidly eliminated from all laboratory animals studied to date. For example, the half life of PFOS in humans, as mentioned above, is approximately five to seven years compared with only 100 days in rats (Johnson *et al.* 1979b). This tremendous difference in elimination rates not only complicates efforts to extrapolate and apply toxicity

information generated from animal studies, but it also calls into question whether the toxic effects (or lack thereof) observed in animals are even relevant to humans (Steenland *et al.* 2010). The importance of the differences in elimination rates between animals and humans cannot be overstated from a toxicological standpoint. Simply put, if animals eliminate PFCs so rapidly that they are cleared from their bodies before they can produce toxic effects, then animal studies cannot provide the necessary data and information to evaluate the toxic effects and risks for human exposures. For this reason, there is growing concern about applying animal toxicity information to humans. This controversy is heightened by the fact that the molecular events that trigger the toxic effects in animals and humans may be fundamentally different.

It has been proposed that the triggering toxic event in animals is enhanced proliferation of a part of the cell called a peroxisome, which has been shown to alter lipids, liver enzymes, and liver size (Kennedy *et al.* 2004; Lau *et al.* 2007; Loveless *et al.* 2006). Proxisome proliferation and the resulting activation of a nuclear receptor (peroxisome proliferator-activated receptor α [PPARα]) have also been proposed as a mechanism for tumor induction and for the immune and hormonal changes seen in rodents (Lau *et al.* 2007). What is not known is whether the peroxisome increases seen in animals are relevant for human exposures because peroxisome proliferation is generally less apparent in humans (Dewitt *et al.* 2008; Klaunig *et al.* 2003), and its relevance in humans remains unclear (Kennedy *et al.* 2004). While significant differences between animal and human PFC toxicity have been known for some time, federal and state regulators continue to rely on animal data (likely out of habit) for developing toxicity values. Toxicity values form the basis of environmental criteria, which are used to establish "safe" PFC levels in soils, ground and surface water, and fish to be eaten. If humans are more sensitive than animals to the toxic effects, environmental criteria based on animal studies may not be sufficiently protective for humans.

Until recently, scientists had to rely on toxicity studies in animals or epidemiological studies of occupationally exposed workers because information on human exposures in the general population was nonexistent. In the earliest animal studies, PFOA was shown to produce a number of toxic effects, including increased weights of liver, kidney, thymus and spleen; hepatotoxicity; endocrine and immune toxicity; growth retardation; and delayed sexual maturation (Kennedy *et al.* 2004; Lau *et al.* 2004; U.S. EPA 2003). Among these toxic endpoints, liver toxicity was considered to be the most significant and relevant to human exposures because it occurs at a dose much lower than other toxic effects in both

rodents and monkeys (Seacat *et al.* 2002; Lau et al. 2004). In fact, the 2002 Seacat *et al.* study showing liver toxicity in monkeys has become the basis for numerous state regulations and environmental criteria.

In addition to animal studies, epidemiological and medical surveillance studies have been conducted on U.S. workers occupationally exposed to PFCs. Most of these focused on mortality and cancer incidence (Alexander 2001a, 2001b, 2004; Alexander *et al.* 2003; DuPont 2003b, 2006; Gilliland and Mandel 1993; Karns and Fayerweather 1991; Walrath and Burke 1989). In general, no consistent association between serum PFC levels and adverse health effects has been observed. However, many of these studies are now considered to have suffered from experimental design flaws and unintentional biases.

In summary, although much toxicity information has been accumulated over the last decade describing numerous toxic effects PFCs produce in both animals and humans, it has not yet been determined whether the toxic effects are identical or even similar. Before animal studies are used to represent human exposures, it is necessary to first show animals and humans respond to PFCs in the same manner. It is standard toxicological practice to determine whether there are species differences in toxicological responses before applying the dose-response relationship observed in animals to humans. Although it would be a violation of the basic tenant of toxicology to extrapolate animal data to humans in order to derive a toxicity value before verifying that there are no species differences, regulatory agencies have done so in the past because no reliable human data was available. With the C8 Health Project studies, we now have solid human exposure information—as well as illness and disease data—making interspecies comparisons possible. An initial comparison indicates that it may not be appropriate to rely on animal studies because animals appear to respond to PFCs differently than humans for the following three reasons:

- Physiological differences between animals and humans are significant. Animals are able to eliminate PFCs from their bodies within hours or days, while it takes humans many years or decades to clear them completely;
- PFCs appear to target different molecular targets in animals and humans. This suggests that there may be wide variability between species in the mode of toxic action that triggers illness and disease.
- There appear to be major differences between animals and humans in the various types of toxic responses, illness, and disease caused by PFCs. Although it is rare, some chemicals are known to produce much different toxic effects in animals than in humans.

These aspects will be fully investigated in the coming months to determine whether it is scientifically tenable to use the results from animal studies to derive toxicity values and environmental criteria for humans.

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ISSUE PAPER 3

RECENT EPIDEMIOLOGY STUDIES CONFIRM LINK BETWEEN PFC EXPOSURE AND ILLNESS AND DISEASE

By Richard DeGrandchamp

Key Aspects of Recent Epidemiological Studies:

- Early toxicity and epidemiology studies suggested perfluorochemicals (PFCs) may be toxic to animals and humans.
- A more recent, very large, court-ordered series of epidemiological investigations conducted by the "C8 Health Project" has recently investigated the link between PFC exposures and illness and diseases.
- The C8 Project was designed to determine whether any "Probable Link" exists between an exposed population of 70,000 residents who unknowingly drank PFC-contaminated water for more than a decade.
- The C8 Project confirmed a Probable Link between low PFC exposures and pregnancy-induced hypertension, testicular cancer, and kidney cancer.
- One of the most alarming conclusions for health professionals is that PFC-related illness and disease was observed at exposure levels far below those previously assumed to be safe exposures levels and that the adverse health effects confirmed in the C8 Project occurred at levels corresponding to "background" levels in the U.S. general population.

Introduction

For more than a decade, toxicologists have known that PFCs produce numerous, but relatively consistent, toxic responses in laboratory animals (see excellent review by Lau *et al.* 2007). In contrast, early epidemiological studies on human populations that were carried out by 3M and DuPont scientists and focused on their worker populations yielded mixed results and conclusions (Gilliland and Mandel 1993, 1996). While toxicity studies provided insight into many toxicological aspects of PFC-related adverse health effects because they were rigorously controlled, epidemiological studies suffered many limitations due to the small number of worker studies, the limited number of participants in each study, and some well-known biases (i.e., "healthy worker effect"), making their interpretation difficult because morbidity and mortality rates may have been masked. In addition, because many workers were men, it was not possible to study reproductive effects, which more recent studies have shown to be important. In summary, the early epidemiological studies were inconclusive. What is certain is that, regardless of the findings of the early epidemiological studies, few were relevant to PFC-induced illnesses in the general population.

Much of the uncertainty surrounding the potential toxicological effects in humans has now been eliminated as the result of more recent, very large-scale epidemiological investigations that are part of the

C8 Health Project. This project is perhaps the largest and most sophisticated epidemiological effort ever conducted for an environmental chemical. The number of individuals studied in this very large group—termed the "exposed cohort"—dwarfs epidemiological studies for other environmental chemicals. In epidemiological studies, the size of the exposed population is directly proportional to the confidence in the findings of the study. For the C8 Health Project, the total number of residents in the exposed population totaled 69,030. Each resident provided blood samples and medical information to researchers, and the level of participation in each study was very high. Moreover, the study design meets the gold standard of epidemiological investigations, which is to accurately document exposures.

For the C8 Project, each resident provided at least one blood sample in which the PFCs were accurately measured. In contrast, many early epidemiology studies lacked this accurate exposure information, and exposures were estimated with mathematical models based on approximate exposure conditions. The findings from the C8 Project studies now provide convincing evidence of a link between PFC exposure and several illnesses and disease. Moreover, they provide evidence that some PFC-induced illnesses may be occurring even at background levels in the general population. PFCs have been detected in background blood samples of 98% of the general public (non-occupationally exposed civilian U.S. population), and the C8 Project revealed that some PFC-related illnesses occurred at those background levels. Whether these illnesses are widespread and prevalent in the general U.S. population is unknown. However, based on the C8 Project studies, this would not be unexpected.

Overview of the C8 Health Project

The C8 Health Project was initiated in 2005 to investigate illnesses and disease related to PFC exposures in the mid Ohio-West Virginia border area where the Washington Works Teflon manufacturing facility was located in Parkersburg, West Virginia (Frisbee *et al.* 2009; http://www.c8sciencepanel.org/index.html). C8 is a synonym for PFOA, which was the primary PFC of interest. The Project was created, authorized, and funded as part of the class action settlement agreement reached in the case of Jack W. Leach *et al.* v. E.I. du Pont de Nemours & Company (Wood County Circuit Court, filed 10 April 2002; Frisbee *et al.* 2009). The $107-million settlement agreement funded the C8 Project to investigate exposures due to PFOA-contaminated drinking water from six water districts that were operated by DuPont. Although PFOA was the primary chemical of interest, the levels of 10 different PFC congeners were measured in at least one blood sample from each of the 69,030 participating residents. Residents also provided researchers their medical records and other documentation relating to diagnoses or medical conditions. Although self-reported medical conditions were accepted, additional information was gathered to verify illnesses and medical conditions. The steps

researchers took to verify the prevalence of illness in the residential population represents a high scientific standard. Previous epidemiology studies were often based on self-reported medical conditions, which can lead to biased results and conclusions.

The C8 Health Project is generally regarded as a milestone in epidemiology and has already significantly advanced our knowledge of PFC-induced toxicity, illness, and disease in humans. Previous toxicological findings in laboratory animals have been interpreted cautiously because there are well-known physiological differences between animals and humans with respect to PFC-induced toxicity. Likewise, past occupational studies were relatively biased and showed inconsistent results. The C8 Project is the first large study on a "normal" residential population with all ages and genders represented.

The project's primary goal of the study ordered by the court was to determine if there is a Probable Link between PFC exposure and specific diseases. However, additional studies that are now being published in peer-review scientific journals provide much needed additional data about specific toxicological effects, PFC elimination rates from the body, and fate and transport mechanisms (which describe how PFCs move in the environment and how residents are exposed to uncontrolled releases of PFCs into the environment). These findings are only now being assimilated by many different groups of scientists, and they will significantly alter and challenge past theories of how PFCs induce illness and disease. At a minimum, the findings raise provocative questions about the margin of safety for background PFC exposures in the general population (i.e., the difference between current background PFC blood levels and toxic blood levels). It is expected that the C8 Project will have both immediate and long-term impacts on environmental regulations. Specifically, the C8 Project findings should prompt a review of whether current state regulations and environmental criteria are truly protective and urge states without environmental standards for PFCs to enact them.

Key Aspects of the C8 Health Project and Major Epidemiological Findings

Most health-related studies conducted as part of the C8 Project were epidemiological studies that compared the prevalence rates of specific illnesses to precisely measured PFC blood levels in each resident. This comparison formed the basis for determining whether PFC exposure could have "caused" those illnesses. Although a "cause-effect relationship" between PFC exposure and illness could not be directly addressed due to limitations of the experimental design, a Probable Link was based on increased prevalence of illnesses with increased PFC levels in residents. This "dose-response" relationship is one of the hallmarks to establish causation.

Although little attention was devoted to characterizing the PFC concentrations in the residents with regard to normal background levels, it is apparent that for some PFC congeners, the participants' levels were indistinguishable from the general U.S. population "background" levels. Background levels are established by the Center for Disease Control and Prevention (CDC), which collects blood and urine samples from a representative population to represent the general U.S. public as part of its ongoing National Health and Nutrition Examination Survey (NHANES: http://www.cdc.gov/nchs/nhanes.htm). With this survey, CDC has identified specific toxic chemicals for analysis so that scientists can determine if exposure to environmental chemicals is at toxic levels and may pose risks in the general population. This chemical-specific data, which is often used to make regulatory decisions to protect public health, is compiled in CDC's National Report on Human Exposure to Environmental Chemicals (http://www.cdc.gov/exposurereport/). The CDC report presents vital chemical-specific body burdens for the general population, which can be used to ensure they do not exceed toxic levels. However, no study has evaluated the cumulative toxic effects associated with the sum total of environmental chemicals that are present in the general population. Over the years CDC has been measuring environmental chemicals in the general population, PFC levels have been significantly elevated but slowly decreasing as PFC production has been reduced. No regulatory or health agency has made a determination on whether those PFC levels pose a risk to the general population. The findings from the C8 Project now provide insight into that very important question.

A review of the PFC blood levels in the C8 Project residents shows that although they were exposed to PFOA, the exposures resulted in only about a six-fold increase when compared with background levels in the general population (32.91 compared with approximately 5 ng/mL). In contrast, the geometric mean PFOS blood level found in the exposed residents was actually lower than that measured by CDC in the general background population (the blood level was 36.8% lower than the 1999-2000 NHANES level and 7.1% lower than the 2003-2004 level). Despite finding that PFOS blood levels were not elevated, researchers included PFOS in their epidemiological studies to evaluate whether PFOS (essentially at background levels) was associated with any illness or disease in the resident population. This decision will prove to be very fortuitous because the findings for PFOS provide insight into what illnesses could be present in the general population due to PFOS exposure and should drive discussions for national public health policy regarding background PFOS exposures. That is, if a probable link exists between PFOS levels in the residents and the residents' levels are at background levels (or below), some members of the general population may already be suffering from illnesses associated with their PFOS body burden. It is not currently known whether PFOS is causing health problems in the general population because no studies have been conducted to address that question.

Since researchers in the C8 Project started publishing their studies on PFC-related illness and diseases, scientists have been surprised at the number of diverse illnesses reported that had not been previously recognized as associated with PFC exposure. Project Experts have published more than 18 peer-review studies since the project began and have investigated many adverse health effects (all of which are summarized in Appendix Table 1). Their studies have clearly demonstrated that exposed residents with elevated PFC blood levels have the following conditions:

- Liver damage;
- Higher rates of attention deficit/hyperactivity disorder (AD/HD);
- Delayed onset of sexual maturation;
- Blood levels that are 141 times the drinking water concentration;
- Increased total cholesterol and low-density lipids in their blood;
- High levels of uric acid in their blood (which is associated with gout and cardiovascular disease);
- Increased rates of testicular and kidney cancer; and
- Have pregnancy-induced hypertension (can lead to serious complications during pregnancy).

In addition to these serious adverse health effects, the researchers have shown that children have significantly higher PFC body burdens than do their biological mothers. It is not known if the children are exposed to more PFCs or if they are not physiologically able to eliminate them as fast as adults. Regardless, it is clear from this singular finding that children need special safeguards as a sensitive subgroup when regulatory agencies develop environmental criteria and public health policy.

In addition to peer-review studies, the C8 Expert Panel has begun issuing its court-ordered Probable Link conclusions, which are summarized in Appendix Table 2. Although the C8 Project team has published numerous studies showing many PFC-related health effects, it should be noted that in order to take the next step and make a determination of a Probable Link between PFC exposure and specific disease, all Project Experts must be in complete agreement and have little doubt remaining. In other words, a Probable Link determination means that the relationship between cause and effect is as close to scientific certainty as scientists can (but rarely do) achieve. To date, the Experts have reached consensus and rendered a Probable Link determination on the following six PFC-related health issues:

- Cancer;
- Diabetes;
- Birth Defects;
- Pregnancy-Induced Hypertension and Preclampsia;
- Miscarriage or Stillbirth; and
- Preterm Birth and Low Birth Weight.

Within these six health issues, they have found a Probable Link for:

- Pregnancy-Induced Hypertension;

- Testicular Cancer; and
- Kidney Cancer.

With the Probable Link determination threshold set so high and the resident's blood levels relatively low, it is surprising that the Experts were able to conclude a Probable Link for any adverse health effect. It should also be noted that because some diseases and illnesses require a latency period (the interval between the beginning of chemical exposure and the onset of the disease), some diseases—such as some forms of cancer—may not detectable in the C8 residents for years to come. The other limitation imposed on the Expert Panel is that they had no choice but to conduct a "cross-sectional" study (also called a "health survey"). Cross-sectional studies are based on a simple "snapshot" review of the health effects that exist at the time the snapshot was taken. Inferential causality (or cause and effect) is sometimes difficult to establish in such studies because the Experts can only measure the "prevalence" of a health effect that exists at the time the snapshot was taken. Study designs such as "longitudinal" studies are better able to determine cause-effect because the "incidence" of a health effect, which refers to new cases of disease triggered with increasing exposure, can be measured. With cross-sectional studies, causality can only be addressed by showing that the residents who had the highest PFC levels also had the highest prevalence of a particular health effect, and that a strong association appears to exist between the two. It cannot be concluded that the high PFC levels caused the effect. These are well-known shortcomings of the type of study design imposed by the court on the C8 Project and were noted by the authors in each study published.

Public Health Implications of C8 Project Findings

When taken as a whole, the C8 Project findings pose unique challenges to health professionals engaged in developing environmental criteria for point source releases and establishing safe exposure levels for the general public. Since numerous health effects were identified among residents whose PFOA levels were only 20 times the background level found in the general population, it could rationally be concluded that even background exposures to PFCs in ambient air and food may exceed acceptable levels. That means that any additional exposures above background exposures from any point source of PFCs may far exceed "acceptable levels" on which all environmental criteria are based (if background levels already pose a risk). Acceptable regulatory levels should take into account the PFC background levels, which are already elevated, in the general public. The C8 studies indicate regulatory criteria should be based on a "margin of safety" approach where additional exposures from a point source are added to the already elevated body burden levels in the general public

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APPENDIX

TABLE 1.

PUBLICATIONS FROM THE C8 HEALTH PROJECT

Publication Title, Authors, and Citation	Purpose of study	Conclusion
Serum Perfluorooctanoate (PFOA) and Perfluorooctane Sulfonate (PFOS) Concentrations and Liver Function Biomarkers in a Population with Elevated PFOA Exposure Gallo V, Leonardi G, Genser B, Lopez-Espinosa M-J, Frisbee SJ, Karlsson L, Ducatman AM, Fletcher T. Environ Health Perspect. 2012 Jan	Determine if PFC exposure causes liver damage	PFCs cause liver damage. The results show a positive association between PFOA and PFOS concentrations and serum alt level, a marker of hepatocellular damage.
Relationships of Perfluorooctanoate and Perfluorooctane Sulfonate Serum Concentrations Between Child-Mother Pairs in a Population with Perfluorooctanoate Exposure from Drinking Water Mondal D, Lopez-Espinosa M-J, Armstrong B, Stein CR, Fletcher T. Environ Health Perspect. 2012 Jan 23	Determine relationship between mother-child PFC serum concentrations. Examine how child:mother ratio varies with child's age, child's sex, drinking-water PFOA concentration.	Concentrations of both PFOA and PFOS tended to be higher in children than in their mothers and persisted until they were about 12 years of age for PFOA and at least 19 years of age for PFOS.
Serum Perfluorinated Compound Concentration and Attention Deficit/Hyperactivity Disorder in Children 5–18 Years of Age Stein CR, Savitz DA. Environ Health Perspect. 2011 Oct;119(10):1466-1471.	Determine if PFCs attention deficit/hyperactivity disorder (AD/HD).	Observed an inverted j-shaped association for AD/HD for PFOA, increased prevalence for PFHXS, and a modest association between PFOS.
Retrospective exposure estimation and predicted versus observed serum perfluorooctanoic acid concentrations for participants in the C8 Health Project Shin H-M, Vieira VM, Ryan PB, Steenland K, Bartell SM. Environ Health Perspect. 2011 Dec;119(12):1760-1765.	Estimate historical PFOA exposures and serum concentrations for 45,276 non-occupationally exposed residents.	Serum PFOA concentrations predicted by exposure models correlated well with observed 2005-2006 human serum concentrations.
Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with age of puberty among children living near a chemical plant. Lopez-Espinosa M-J, Fletcher T, Armstrong B, Genser B, Dhatariya K, Mondal D, Ducatman A, Leonardi G. Environ Sci Technol. 2011 Oct 1;45(19):8160-6. Epub 2011 May 2.	Investigate whether perfluorooctanoic acid (PFOA) and PFOS impacted sexual maturation.	PFCs delay the onset of puberty.

Publication Title, Authors, and Citation	Purpose of study	Conclusion
Comparison between free serum thyroxine levels, measured by analog and dialysis methods, in the presence of perfluorooctane sulfonate and perfluorooctanoate. Lopez-Espinosa M-J, Fitz-Simon N, Bloom MS, Calafat AM, Fletcher T. Reprod Toxicol. 2011 Apr 17. [Epub ahead of print]	Determine if differences between human ft4 measurements in serum by an analog versus dialysis method in presence of PFOS or PFOA.	No measurement bias between analog and dialysis method.
Environmental fate and transport modeling for perfluorooctanoic acid emitted from the Washington Works Facility in West Virginia. Shin H-M, Vieira VM, Ryan PB, Detwiler R, Sanders B, Steenland K, Bartell SM. Environ Sci Technol. 2011 Feb;45(4):1435-1442. Epub 2011 Jan 12	Evaluate different fate and transport models .	High correlation between predicted versus observed water concentrations.
Private drinking water wells as a source of exposure to PFOA in communities surrounding a fluoropolymer production facility. Hoffman K, Webster TF, Bartell SM, Weisskopf MG, Fletcher T, Vieira VM. Environ Health Perspect. 2011 Jan;119(1):92-7. Epub 2010 Oct 4	Assess biomagnification of PFOA from drinking contaminated water from private wells.	Each 1 µg/l increase in PFOA levels in drinking water was associated with an increase in serum concentrations of 141.5: the serum:drinking-water biomagnification factor was 114.
Accumulation and clearance of PFOA in current and former residents of an exposed community. Seals R, Bartell SM, Steenland K. Environ Health Perspect. 2011 Jan;119(1):119-24.	Evaluate elimination from body based on PFOA concentration in drinking water.	Serum PFOA half-lives were 2.9 and 8.5 years for water districts with higher and lower exposure levels.
Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adolescents: Results from the C8 Health Project. Frisbee SJ, Shankar A, Knox SS, Steenland K, Savitz DA, Fletcher T, Ducatman AM. Arch Pediatr Adolesc Med. 2010 Sep;164(9):860-9.	Evaluate PFOA and PFOS effects on serum lipids in children and adolescents.	Increasing PFOA and PFOS were associated with elevated total cholesterol and ldl.
Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA). Steenland K, Fletcher T, Savitz DA. Environ Health Perspect. 2010 Aug;118(8):1100-8. Epub 2010 Apr 27	Presents a review of the past epidemiologic literature for PFOA.	Past epidemiologic evidence does not permit causality to be addressed.
Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA. Steenland K, Tinker S, Shankar A, Ducatman A. Environ Health Perspect. 2010 Feb;118(2)229-33.	Determine if PFOA and PFOS increase uric acid levels.	Higher serum levels of PFOA were associated with a higher prevalence of hyperuricemia, which can lead to gout and high blood pressure.
Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Bartell SM, Calafat AM, Lyu C, Kato K, Ryan PB, Steenland K. Environ Health Perspect. 2010 Feb;118(2):222-8.	Determine the half-life of PFOA after installing charcoal filters.	PFOA had a half-life of 2.3 years in the body in first year.

Publication Title, Authors, and Citation	Purpose of study	Conclusion
The C8 Health Project: Design, methods, and participants. Frisbee SJ, Brooks AP Jr, Maher A, Flensborg P, Arnold S, Fletcher T, Steenland K, Shankar A, Knox SS, Pollard C, Halverson JA, Vieira VM, Jin C, Leyden KM, Ducatman AM. Environ Health Perspect. 2009 Dec;117(12):1873-1882. Epub 2009 Jul 13.	Report the methods and blood results from the c8 health project.	Project is the largest known population study of community PFC exposure permitting evaluations of associations between PFOA and disease.
A cross-sectional analysis of type II diabetes in a community with exposure to perfluorooctanoic acid (PFOA). MacNeil J, Steenland NK, Shankar A, Ducatman A. Environ Res. 2009 Nov; 109(8):997-1003.	Determine if PFOA causes increased diabetes mortality.	No association between PFOA and either type ii diabetes or fasting glucose.
Association of perfluorooctanoic acid and perfluorooctane sulfonate with serum lipids among adults living near a chemical plant. Steenland K, Tinker S, Frisbee S, Ducatman A, Vaccarino V. Am J Epidemiol. 2009 Nov 15;170(10):1268-78. Epub 2009 Oct 21.	Determine if PFOA cause s increase in uric acid.	Higher serum levels of PFOA were associated with a higher prevalence of hyperuricemia, which is a risk factor for hypertension and cardiovascular disease.
Serum levels of perfluorooctanoic acid and perfluorooctane sulfonate and pregnancy outcome. Stein CR, Savitz DA, Dougan M. Am J Epidemiol. 2009 Oct 1;170(7):837-846. Epub 2009 Aug 19.	Evaluate effects of PFOA and PFOS on reproduction.	PFOA produced modest association for preeclampsia and birth defects and PFOS for preeclampsia and low birth weight, but associations were small, and based solely on self-reported health outcomes.
Predictors of PFOA levels in a community surrounding a chemical plant. Steenland K, Jin C, MacNeil J, Lally C, Ducatman A, Vieira V, Fletcher T.	Evaluate exposure conditions and lifestyle on PFC levels.	PFOA levels in this population varied with distance of residence from the plant and employment at the plant. Effects of demographic and lifestyle covariates were relatively weak.

TABLE 2.

COURT ORDERED PROBABLE LINK FINDINGS

TYPE OF EVALUATION	SUMMARY OF PROBABLE LINK FINDINGS
CANCER	On the basis of epidemiologic and other data, the C8 Science Panel concluded there is a probable link between exposure to PFOA and testicular cancer and kidney cancer but not any of the other cancers that were considered.
DIABETES	On the basis of epidemiologic and other data, the C8 Science Panel concluded there is no probable link between exposure to PFOA and Type II (adult-onset) diabetes.
BIRTH DEFECTS	Birth defects are structural malformations in the infant that arise during fetal development. Limited evidence for an increased risk of congenital heart defects with increased estimated serum PFOA was observed in one study, but the Science Panel considered this most likely to be due to chance. In the other studies, either no meaningful associations were found or specific types of birth defects could not be examined due to the small population size. On the basis of epidemiologic studies and other data, the C8 Science Panel concluded there is not a probable link between exposure to PFOA and birth defects.
PREGNANCY-INDUCED HYPERTENSION AND PREECLAMPSIA	Pregnancy-induced hypertension is defined as significantly elevated blood pressure that begins after the 20th week of pregnancy. Preeclampsia is a specific type of pregnancy-induced hypertension, which is accompanied by leakage of protein into the urine. There was also evidence of an association between estimated serum PFOA and pregnancy-induced hypertension based on the continuous exposure indicator. Measured serum PFOA was weakly and irregularly associated with preeclampsia, an association that was strengthened when the analysis was restricted to more recent pregnancies. On the basis of epidemiologic and other scientific data, the C8 Science Panel concluded there is a probable link between exposure to PFOA and pregnancy-induced hypertension.
MISCARRIAGE OR STILLBIRTH	Pregnancy loss refers to miscarriage and stillbirth, the former defined as loss of pregnancy before 20 weeks of gestation and the latter at 20 weeks gestation or later. On the basis of epidemiologic and other scientific data available to the C8 Science Panel, the conclusion is that there is not a probable link between exposure to PFOA and miscarriage or stillbirth.
PRETERM BIRTH AND LOW BIRTH WEIGHT	Preterm birth is defined as early delivery of an infant before completing 37 weeks of gestation. Most studies found no association between preterm birth and measured or estimated serum PFOA. An association with early preterm birth and estimated PFOA was found in one study, although the sample size was small. The results from the studies of other populations found little or no association between measured serum PFOA and preterm birth. On the basis of epidemiologic and other scientific data by the C8 Science Panel, the conclusion is that there is not a probable link between exposure to PFOA (C8) and preterm birth or low birth weight.

Issue Paper 4

Increased Disease Prevalence in the U.S. Population Is Linked to Environmental Chemical Exposure

By Dr. Richard DeGrandchamp

Debilitating illnesses and disease have markedly increased in the general United States (U.S.) population over the last three decades. A substantial number of scientific studies have now confirmed links between a number of these illnesses and widespread chemical exposures among the general population of the U.S. It is indisputable that uptake and bioaccumulation of toxic chemicals in the bodies of Americans has paralleled the rise in prevalence of numerous diseases. In addition to the links between chemical exposure and disease that have already been identified, credible evidence suggests that "silent epidemics" that have not yet been identified are also developing (Landrigan *et al*. 2011; Landrigan *et al*. 2012). That is, body burdens of chemicals that are known to produce specific diseases have reached such high levels in the general population that it is likely that they are increasing the prevalence of specific diseases. Unfortunately, the studies necessary to prove that link have not yet been conducted. Although illnesses and diseases have been increasing for the last 30 years in the general U.S. population, it is particularly troubling that the greatest increases have disproportionately affected children and adolescents. This segment of the general population has experienced an alarming rise in disease and illnesses that are now at epidemic levels (Woodruff *et al.* 2004; Landrigan *et al.* 2011). Some examples of childhood diseases that are on the rise include the following:

- **Asthma:** It is one of the most common chronic diseases among American children, and the prevalence of childhood asthma has more than doubled over the past 20 years. In 2008, 9% of all U.S. children had asthma (Environmental Protection Agency [EPA] 2010; Federal Interagency Forum on Child and Family Statistics 2010).
- **Birth Defects:** These are now the leading cause of infant death, and some defects that occur in male reproductive organs and the abdominal wall have increased in frequency (Paulozzi *et al*. 1997; Vu *et al*. 2008).
- **Leukemia and Brain Cancer:** These diseases steadily increased in children younger than age 18 from the 1970s through the 1990s (National Cancer Institute 2012).
- **Neurodevelopmental Disorders:** These include dyslexia, mental retardation, attention deficit hyperactivity disorder (ADHD), and autism. Autism spectrum disorder (ASD) is now at epidemic rates, and it is diagnosed in one of every 88 American children. The prevalence of ADHD has also risen. Today, 14% of U.S. children have been diagnosed with this condition, and two-thirds of them also have learning disabilities (Pastor and Reuben 2008; Boyle *et al.* 2009).
- **Immune Disorders:** Immunotoxicity has now been shown to occur in the general population due to background exposure to perfluorinated compounds (PFCs). Significant toxic effects on children's immune systems are now shown to interfere with routine

> childhood immunizations in children, leaving them predisposed to infection and disease (Grandjean *et al.* 2012).

Recognizing that children are uniquely susceptible to disease and illness due to environmental causes, two notable major research initiatives are now underway in the U. S. and Japan (Landrigan *et al.* 2006; Kawamoto *et al.* 2011; National Institutes of Health [NIH] 2012). The U.S. study is led by the NIH, with a consortium of scientists from the National Institute of Environmental Health Sciences (NIEHS) unit of the NIH, Centers for Disease Control and Prevention (CDC), and EPA. Links between childhood disease and chemical exposures will be studied over a 20-year period, following neonates until they become adults. While health professionals hail this effort, findings from these studies will not become available for several years. This is important because an epidemic of behavioral and learning disorders has been affecting school-aged children and adolescents for the last three decades (Pastor and Reuben 2008; U.S. Department of Health and Human Services 2003; U.S. Department of Education 2007; Kelleher *et al.* 2000; Grupp-Phelan *et al.* 2007). Educators have reported a rise in the number of children with these disorders, and pediatricians have also reported an increased number of pediatric outpatient visits related to behavioral and emotional disorders (CDC July 2008; Federal Interagency Forum on Child and Family Statistics. 2012; DHHS 2003; U.S. Department of Education 2007; Kelleher *et al.* 2000; Grupp-Phelan *et al.* 2007).

Although we now know that children are much more vulnerable to the toxic effects of environmental chemicals than are adults, this was not always so. The National Academies of Sciences (NAS) National Research Council (NRC) report *Pesticides in the Diets of Infants and Children* (NAS 1993) was a watershed study that first recognized that neonates and developing children are quantitatively and qualitatively different from adults in their sensitivity to toxic chemicals. Prior to this report, health professionals simply considered children to be "little adults," and it was widely assumed children and adults suffered similar toxic effects at the same doses. Historically, this assumption placed children at risk from chemical exposures because health policy and environmental criteria were based on the effects for an "average adult." Indeed, many regulatory criteria ignore major physiological differences between children and adults, and continue to be developed for adults.

Although adjustments are made for differences in size and chemical intake, it is naïve to believe a safe level for an adult can be so easily adjusted to protect children. Children do not detoxify chemicals or eliminate them from their bodies as rapidly as adults. Children's developing organs are largely unprotected from the chemicals they absorb into circulating blood. Decades of research in pediatrics and

developmental toxicology have now shown that, as organs rapidly develop during childhood, there are "windows of vulnerability" when even minute chemical exposures to toxic chemicals—levels that would have no adverse effects on adults—can disrupt development and lead to irreversible and permanent functional and behavioral impairment (Rodier 1995; Diamanti-Kandarakis *et al.* 2009). Although all developing organ systems can be damaged during development, the brain is particularly vulnerable because billions of brain cells are making vital connections, and it is not protected by a functioning blood-brain barrier. This physical barrier prevents toxic chemicals from reaching the brain in adults, but is not fully functional in the fetus or neonate until after birth during the fist year. Before this time, toxic chemicals easily move from the blood into the brain and disrupt the highly sensitive architecture and function of billions of brain cells that are undergoing rapid division and development to form neural circuits.

There are now between 400,000 and 600,000 children with brain disorders of the 4 million children born in the U.S. each year (Landrigan *et al.* 2012). It is now recognized that early chemical exposures that start in the fetus are responsible for many disorders, including ASD. The first studies to firmly establish a link between ASD and chemical exposure were reported with medications—thalidomide, misoprostol, and valproic acid—taken in the first trimester of pregnancy (Arndt *et al.* 2005; Daniels 2006; London *et al.* 2012). ASD has since been linked to prenatal exposures to the organophosphate insecticide chlorpyrifos (Eskenazi *et al.* 2007) and to phthalates (Miodovnik *et al.* 2011). Chorpyrifos is widely used throughout the U. S., and phthalates are added to millions of plastic products to make them softer and easier to mold. Although commercial use of phthalates is declining, the breadth of phthalate contamination and exposures in the U. S. is so vast, and the body burden so high, that the general population will experience toxic effects due to phthalate exposure for many years to come.

Additional prospective epidemiological studies have linked loss of cognition (measured as reduced intelligence quotient, or IQ), dyslexia, and ADHD to lead (Jusko *et al.* 2008), methylmercury (Oken *et al.* 2008), polychlorinated biphenyls (PCBs; Winneke 2011), arsenic (Wasserman *et al.* 2007), manganese (Khan *et al.* 2011), polycyclic aromatic hydrocarbons (PAHs; Perera *et al.* 2009), bisphenol A (Braun *et al.* 2011), brominated flame retardants (Herbstman *et al.* 2010), and PFCs (Stein and Savitz 2011). An expert committee convened by the U.S. National Academy of Sciences estimated that 3% of neurobehavioral disorders are caused directly by toxic environmental exposures and that another 25% are caused by interactions between environmental factors—defined broadly—and inherited susceptibilities (National Research Council 2000).

While gross and obvious medical conditions in the general population are easily recognized, subtle toxic effects like behavioral changes in children can go unnoticed for decades—even when they affect thousands of children. The late Dr. David Rall, former director of the National Institute of Environmental Health Sciences, famously stated (Weiss 1982):

> *If thalidomide [a drug widely used in the 1950s and 1960s to treat morning sickness in early pregnancy] had caused a ten-point loss of IQ instead of obvious birth defects of the limbs, it would probably still be on the market."*

The intent of his statement is that public policy is not typically responsive to public health epidemics in children unless the medical conditions or symptoms are grossly obvious, as they were for children who were born with grotesquely malformed arms and legs after their mothers took thalidomide to prevent nausea or as a sleep aid. The number of children born with missing limbs or severe deformities of their arms or legs was estimated at 10,000 to 20,000 worldwide.

Although we now know that fetuses are exposed to the same chemicals as their pregnant mothers, as recently as 1960, scientists did not know medicines and chemicals could easily pass across the placental barrier and harm the developing fetus (Heaton 1994). Despite the horrific birth defects that shocked the world public health community and that were clearly linked to chemical exposures in the womb, it was not until 1962 that the U.S. Congress finally passed a law requiring that new drugs be tested for fetal effects. It is also noteworthy that even after the painful thalidomide lessons were learned, no regulations or laws currently protect fetuses from chemical exposures due to commercial products. Only those chemicals that are used as food products, medicines, or pesticides are required to undergo toxicity testing for fetal effects. Although scientists have tested some chemicals for fetal toxicity, the vast majority of chemicals used in consumer products have not been tested, and those that have are usually tested for academic reasons and not for regulatory purposes. Even when studies prove that a chemical can produce fetal toxicity or birth defects, no regulations exist to prevent those chemicals from being used by industry in commercial products.

Autoimmune diseases are at epidemic levels. Although several of these diseases are well known by the general public, autoimmune diseases are actually a family of more than 100 chronic, and often disabling, illnesses. Autoimmunity is initiated when one's immune system becomes overactive. Rather than

destroying foreign invader cells, such as bacteria and viruses, the defective immune system attacks one's own healthy cells and tissues, causing a variety of different autoimmune effects.

While some autoimmune disease is not as well known as other diseases, it collectively affects an estimated 24 million Americans, which is more than the 9 million who develop cancer or the 22 million with heart disease (NIH 2005). Autoimmune diseases can affect virtually every site in the body, including the endocrine system, connective tissue, gastrointestinal tract, heart, skin, and kidneys. Some of the more common autoimmune diseases include rheumatoid arthritis, type 1 diabetes mellitus (T1D), multiple sclerosis, celiac disease, and inflammatory bowel disease. Organ-specific autoimmune diseases are characterized by immune-mediated injury localized to a single organ or tissue—for example, the pancreas in T1D and the central nervous system in multiple sclerosis. In contrast, non-organ-specific diseases, such as systemic lupus erythematosus (referred to as lupus), are characterized by immune reactions against many different organs and tissues, which may result in widespread injury and premature death.

Autoimmune disease disproportionately affects women. It is one of the top 10 causes of death and the second-highest cause of chronic illness in U.S. women under the age of 65. Autoimmune diseases have been reported to be on the rise in the U.S. and around the world, making this poorly understood category of disease a public health crisis at levels comparable to heart disease and cancer (NIH 2011). One of the major clinical issues that have plagued investigators and epidemiologists is that there are few standardized diagnostic clinical tests that can be used to determine prevalence (all cases) or incidence (newly diagnosed cases) in the U.S. Nevertheless, some studies have shown the number of persons affected by specific autoimmune diseases to be rising dramatically. For example, Maahs et al. (2010) reviewed the data on incidence of T1D for 114 populations from 57 countries studies during the time period of 1990-1999 and concluded that T1D has been increasing by 2% to 5% worldwide each year. In the U.S., 25.8 million children and adults in the United States—8.3% of the population—have diabetes.

The prevalence of systemic lupus erythematosus (SLE) has also been identified as an autoimmune disease on the rise in some parts of the U.S. Uramoto *et al*. (1999) analyzed the number of newly diagnosed cases of lupus in Rochester, Minnesota, and found that the incidence of SLE had nearly tripled over the past four decades. No national incidence data are currently available because the specific time of onset of disease is difficult to determine as the first symptoms are non-specific and investigations of clinical records are resource and labor intensive. For this reason, epidemiological studies of SLE are conducted on a small-scale level. Congress recently funded CDC to conduct two population-based SLE registries

with the primary purpose of generating better prevalence and incidence estimates in Michigan (Washtenaw and Wayne Counties) and Georgia (DeKalb and Fulton Counties; CDC http://www.cdc.gov/arthritis/basics/lupus.htm/#2).

Since cures are not yet available for most autoimmune diseases, patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, reduced productivity at work, and high medical expenses. Recognizing this growing epidemic, Congress commissioned the National Institutes of Health, Autoimmune Diseases Coordinating Committee (ADCC) to develop a comprehensive strategic Research Plan to address all forms of autoimmune disease (NIH 2005).

Toxicologists have long been able to identify which target organs are damaged by specific toxic chemicals based on controlled studies of laboratory animals. With laboratory studies, identifying the target body organs and the toxic effects at the molecular level is standard practice. However, extrapolating animal data to predict human toxicity is complex and uncertain due to the significant species differences between animals and humans. Furthermore, subtle toxic effects on behavior and brain development are difficult or impossible to identify in animals simply because animals cannot "communicate" with scientists. Unless an animal's behavior is truly aberrant, symptoms signaling subtle changes in the brain simply go unnoticed. For example, toxicologists cannot study ASD or ADHD in animals because no animal models currently exist. Equally important in translating toxicity information from animal studies to human is the uncertainty that equal chemical doses or exposures will cause the same effects in humans. Consequently, regulatory criteria are based on a "best guess" scenario for many chemicals.

Recognizing the limitations of animal studies and the virtual absence of data and information on actual chemical exposures to Americans, the CDC initiated the National Health and Nutrition Examination Survey, or NHANES (CDC; National Center for Health Statistics 2012). The goal of this program is to collect samples from the general U.S. population in order to 1) Establish the chemical "body burden" for the general (non-occupationally exposed) U.S. population, and 2) Determine if the chemical body burden levels pose a threat to the nation's public health. Implementation of the NHANES studies is widely regarded as one of the most significant scientific advancements in the field of public health.

In the first NHANES study, only a small subset of environmental chemicals was measured in blood, hair, and urine samples. Nevertheless, those results were surprising because few scientists would have

predicted that environmental exposures would have produced such high body burden levels in the vast majority of Americans. In the past 50 years, more than 80,000 new synthetic chemicals have been manufactured (Landrigan and Goldman 2011). Of these, EPA has classified 3,000 "high production volume" (HPV) chemicals that are in widest use and thus pose the greatest potential for human exposure (Goldman 1998). These HPV chemicals are used today in millions of consumer products and are known to have been released generally into the environment and have become known as ubiquitous "anthropogenic" (man-made) contaminants. Due to cost constraints, CDC could only conduct biomonitoring for a small fraction of chemicals on the HPV list. Despite this shortcoming, the NHANES findings were startling for two reasons. First, nearly all of the approximately 200 HPV chemicals CDC measured were detected in the bodies of virtually all Americans, including pregnant women (Woodruff *et al.* 2011). The fact that chemicals were detected in pregnant women is very important because we now know for certain what we could only suspect earlier—human exposure to environmental chemicals starts before birth. Fetal exposures are particularly worrisome because it is at this stage of development that humans are most vulnerable to toxic effects. Second, the body burden levels in the general population directly measured for the more than 2,000 participants representing background levels in the general population were very high, and were much higher than previously assumed.

Prior to the NHANES studies, it was generally assumed (lacking any hard data) that environmental exposures did not pose a health threat to most Americans because "background" exposures were too low. Consequently, efforts to protect citizens from chemicals that pose a risk to human health were limited to occupational exposures in the workplace. In stark contrast, there are no regulatory measures in place to protect the general public. Background body burdens have reached alarming levels that were previously assumed possible only in occupational settings. With the exception of a safe body burden for lead (which CDC has recommended not exceed 10 micrograms per deciliter in children), no state or regulatory agency has ever derived an acceptable body burden for any of the more than 80,000 chemicals currently being used in commerce. Lacking established "safe" body burden levels; scientists and regulators cannot directly determine if the high background levels pose health threats. The only approach available to scientists is to measure the rates of illness and disease, then determine if they are increasing proportionally with increasing chemical concentrations in the NHANES participants. Several recent studies applying this approach have identified two chemical groups that are associated with diabetes.

The prevalence of diagnosed diabetes inexplicably increased by 176% (from 2.5% to 6.9% of the population) from 1980 through 2010 (CDC 2012). Although we now know obesity and a growing older

segment of the U.S. population can account for some of this increase, these two factors alone do not account for all the new diabetes cases. In looking for chemical causal factors, it has now been confirmed that like obesity, an increase in body burden of dioxins and PCBs is also strongly associated with diabetes (Lee *et al.* 2006; Lee *et al.* 2007; Everett *et al.* 2007; Kang *et al.* 2006; Rylander *et al.* 2005; Fierens *et al.* 2003; and Cranmer *et al.* 2000).

Likewise, an increasing body burden of phthalates has now been shown to significantly increase the risk of developing diabetes. Phthalates are known as endocrine disruptors (mimicking hormones) and are ubiquitous in commercial products (Crinnion 2010; Hauser and Calafat 2005; Romero-Franco *et al.* 2011). They are used in millions of different food packaging items, cosmetics, perfumes, nail polishes, flooring, and other industrial products. Over the past 50 years, phthalate production and use in commercial products has dramatically increased (Baillie-Hamilton 2002) and phthalates are now detected in more than 75% of the U.S. population (Hauser and Calafat 2005). Women in particular, have much higher body burden levels compared with men, possibly due to higher use of personal care products. This increased exposure to phthalates has paralleled the increase in diabetes in the female population. American women experienced a doubling of diabetes rates between 1980 and 2010, with prevalence increasing from 2.9% to 5.9% (CDC 2012). The doubling of diabetes prevalence parallels the near doubling of diabetes found in women with high phthalate levels compared with women who had low levels (James-Todd *et al*. 2012).

Now that scientists have access to the NHANES database, a concerted effort is underway by numerous academic and scientific groups, as well as regulatory agencies, to identify other links between "background" exposure levels and the significant rise in illness and disease. The importance of NHANES data cannot be overstated because the biomonitoring data have become a "canary in the coal mine." We no longer have to assume or predict the levels of environmental chemicals based on animal studies or complex mathematical models of exposure.

In addition to establishing links between illness and the chemical body burdens from the NHANES database, scientists have now shown that the background levels in a specific residential population in Ohio also had increased rates of illness and disease due to PFCs used in hundreds of common household products. This residential population was not exposed to any specific point releases. Nevertheless, illness and disease were found to be elevated and were strongly associated with background exposure levels (Stein and Savitz 2011; Lopez-Espinosa 2011; Frisbee 2011).

Scientists are concerned that many in the general public may already be unknowingly experiencing illness and disease in a silent epidemic yet to be identified (Grandjean and Landrigan 2006). It is possible that there are synthetic chemicals whose toxicity to early childhood development has not yet been linked to any particular chemical among the hundreds of untested chemicals currently in wide commercial use. Significant and obvious medical conditions that develop in the general population are relatively easy to identify, but as previously noted, subtle toxic effects like behavioral changes in children can go unnoticed for decades.

Contrary to the generally held belief by the public that governmental regulatory agencies rigorously study and protect the U.S. general population from the toxic effects of the more than 80,000 chemicals now in use in consumer products, this is a misplaced assumption. The vast majority of those chemicals in use today have never undergone toxicological testing. Regulations only require chemicals intended to be used as a food product, medicine, or pesticide to undergo toxicological testing. In addition, many chemicals used in consumer products remain undisclosed. Content information is often shielded by "proprietary information" exclusions. Lacking toxicity information on most chemicals forces scientists to wait until there is an outbreak of illness, and only then is it possible to link the illness or medical condition to chemical exposure, essentially using the general population as "human guinea pigs." Public health professionals must simply wait for a "silent epidemic" to reach a critical mass of sufficient size that it captures the public's attention and investigations are demanded.

However, even when studies are initiated to identify links, the conventional scientific approach whereby the rate of illness in a control group (which has not been exposed to the chemical) is compared with that of the exposed group is not possible. This is because, as the NHANES findings clearly show, nearly all Americans have detectable concentrations of the approximately 200 environmental chemicals that have been measured. Simply put, there is no "control group," since all Americans have been exposed. Thus, comparisons must be made between those who have "low" body burdens and those who have "high" body burdens. This makes it difficult to prove an association between chemical exposure and illness, which can allow a silent epidemic to continue.

A well-known example of a silent epidemic and one of the greatest failures of public health professionals to protect the young involved childhood lead poisoning resulting from leaded gasoline (Goldman *et al.* 2004). For approximately 50 years (1925 to 1970), petroleum manufacturers added tetraethyl lead to

gasoline to improve mileage and engine efficiency. As a result, widespread lead exposure occurred throughout the U.S., resulting in children's blood lead levels that far exceeded safe levels. Hundreds of thousands of children developed neurological damage. Symptoms of lead toxicity included behavior disorders, learning disabilities, and reduced intelligence. A silent epidemic raged before it could be proven that these disorders were associated with the common use of leaded gasoline (Needleman *et al.* 1979). It is noteworthy, however, that the main driving force for the phase out was not concern for public health, but commerce; lead was found to damage automobile catalytic converters. Widespread lead contamination and exposures occurred throughout the U.S. for more than 30 years before enough children were diagnosed with brain damage that the silent epidemic was finally heard and steps were taken to protect the general public.

Regulators and public health agencies should take immediate steps to reduce the already high body burdens in the general population. Based on the NHANES data, it is obvious that current regulatory efforts to protect Americans from bioaccumulating chemicals in their bodies are not working. For this reason, many health professionals have begun to call for a complete and radical overhaul of the regulatory process that currently allows chemicals that have not undergone toxicological testing to be used in commercial products and released into the environment (Landrigan *et al.* 2011). Regulatory agencies must operate in reactionary mode to clean up and remove chemicals released into the environment. Despite claims from chemical manufacturers and commercial users of chemicals in industry that they are over-regulated, no industry is actually required under any state or federal law to conduct independent toxicity studies before chemicals are used in commercial products.

The only law that applies to toxicity testing of commercial products is the Toxic Substances Control Act (TSCA) of 1976. The intent of the law when it was passed was to evaluate the toxicity of chemicals already in use and to require premarket toxicological evaluation of all new chemicals before they are produced and widely used in commercial products. Unfortunately, the law failed to achieve both these admirable goals because Congress "grandfathered in" approximately 62,000 chemicals already on the market, precluding any toxicity testing of chemicals in use at the time (EPA 2012; Goldman 2002). These chemicals were simply presumed to be safe and allowed to remain in commerce, unless and until the EPA made a finding that they posed an "unreasonable risk." In theory, this may seem a reasonable approach to regulating chemicals, but in practice EPA has found it nearly impossible to prove such a finding. Even though many chemicals used commercially are known human carcinogens and have been shown to produce severe toxicity in humans, including neonates and children, EPA has only met the

burdensome proof requirement to remove five chemicals from commercial use over the last 35 years. These chemicals are PCBs, chlorofluorocarbons, dioxin, asbestos, and hexavalent chromium. No other federal or state agency has the legal authority or regulatory mechanism to eliminate or even reduce chemical exposures to the general public. EPA and state regulatory agencies can only respond to uncontrolled releases after they occur in the environment and only when they pose an imminent threat to human health or the environment. Many studies have looked at the life-cycle of environmental chemicals—starting with their synthesis until the ultimate human exposure—and show a "preventive" approach would obviously preclude the pain and suffering of those effected but would also save the U.S. billions in health care costs (Landrigan *et al.* 2002). For example, in addition to the emotional and societal impacts ASD has on affected children and their families, this disorder also places an incredible economic burden on the national health care system. Based on conservative estimates of the prevalence of ASD in the U.S., it was estimated that the annual societal ''cost of illness'' for ASD was between $36 billion and $52 billion in 2005 dollars.

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Issue Paper 5

Recommendations

By Robert Delaney

The bottom line conclusions from this report are the following.

- There is convincing evidence that the rates of autoimmune diseases and neurologic disorders are on the rise in the human population of the United States (U.S.) and there is no reason to believe that Michigan is exempt from this fact.
- There is currently no organized or consistent monitoring of trends in the rates of the autoimmune diseases and neurologic disorders in Michigan; therefore, there is no system in place to address these trends.
- These increased rates are the result of actual changes in the health of our population as a result of environmental factors, and are not just the result of improved health monitoring.
- There are several widely dispersed families of chemicals in the environment that are suspected of possibly causing these increases in human health impacts.
- Not only are human populations exposed to these contaminants, but also there is widespread exposure to the nation's and to Michigan's ecosystems by these chemicals.
- There is little data on the nature and extent of many of the contaminants in the environment that are the possible causes of these health effects.
- One family of contaminants that are widely distributed in Michigan's environment, that are contained in the blood serum of virtually every Michigan citizen and that are included in the list of suspect chemicals causing the above mentioned health effects are the perfluoroalkyl chemicals (PFCs).
- The former Wurtsmith Air Force Base (WAFB) is currently the only identified point source of PFC contamination in Michigan. The operations of the base resulted in very widespread PFC contamination of groundwater, surface water, and biota in the Oscoda area.
- There will be many other sites in Michigan that contain high levels of PFCs in the environment and in biota and potentially in citizens of the state.

Given the above, these are some recommendations on what the departments should do.

From my perspective, the first thing that needs to be done is to convince the upper management of the Michigan Department of Environmental Quality (MDEQ) (and eventually the Michigan Department of Community Health [MDCH], Michigan Department of Agriculture and Rural Development [MDARD], and Michigan Department of Natural Resources [MDNR]) that there is a statewide human health crisis occurring with regard to increases in the autoimmune and neurologic disorders. The crisis likely has its roots in chemicals that are in the general environment (both natural and anthropogenic environment) that are regulated by the departments.

I recommend that the Director of MDEQ and key upper level managers receive a briefing from the following three people.

- Dr. Richard DeGrandchamp of the University of Colorado, author of three of these papers
- Dr. John Meeker, Professor of Epidemiology at the University of Michigan
- Dr. Deb MacKenzie-Taylor toxicologist for the MDEQ

I have confidence in the independence, knowledge, and intellectual integrity of these three people. I would want them to brief the Director on the evidence of the magnitude of these diseases and trends in prevalence of these diseases, and the information linking contamination of our food supply/environment to these diseases. If the Director is putting the prestige and authority of his office behind an effort, he needs complete confidence that there is a true crisis.

Once the MDEQ Director is satisfied of the high likelihood that there is such a crisis, then he, in my view, should contact the Directors of MDARD, MDCH, and MDNR and have them briefed on these findings. Either that or he should deal directly with the Governor.

If interdepartmental collaboration can be established, then a "blue ribbon" focus group should be formed from academia and the departments to review the situation, create white papers estimating the risks, the data gaps, needed studies, cost/benefit analysis of regulatory actions, adequacy of the existing laws, processes to deal with the situation, and propose appropriate risk reduction measures that could be implemented. Existing processes and laws seem inadequate to address even the human health crisis, let alone any environmental impacts that are occurring. Below are the suggested members of the focus group. I do not know many of these people. Many have just been recommended to me by internal staff or by other scientists. More thought should go into the list before any decisions are made.

Contact information for these individuals is attached.

Potential Focus Group Members (Technical Members)

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- John Buchweitz
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- Christina Bush
  MDCH
  Toxicologist
- Dr. George Corcoran, Ph.D.
  Chairman and Professor
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  Eugene Applebaum College of Pharmacy and Health Sciences
  Wayne State University
- Richard L. DeGrandchamp, Ph.D.
  Part-time Instructor
  University of Colorado
  Department of Geography and Environmental Sciences
  University of Colorado Denver
  President, Scientia Veritas, L.L.P.

- Dr. James Hartman
  Director
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  DOD REC Region 5
- Dr. Ronald Hites
  Distinguished Professor
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  School of Public and Environmental Affairs
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- Dr. Howard Hu, M.D., M.P.H., Sc.D.
  NSF International Department Chair, Environmental Health Sciences
  Professor of Environmental Health Sciences
  Professor of Epidemiology
  Professor of Internal Medicine
  University of Michigan
- Dr. Deborah R. MacKenzie-Taylor
  MDEQ
  Toxicology Specialist
- Rita Loch-Caruso, Ph.D.
  Professor, Environmental Health Sciences
  Professor, Program in the Environment, LS&A
  Associate Research Scientist, Reproductive Sciences Program
  University of Michigan
- Susan Masten, Ph.D., P.E.
  Professor
  Civil and Environmental Engineering
  Michigan State University
- Dr. John Meeker, Sc.D., C.I.H.
  Associate Professor
  Environmental Health Sciences
  University of Michigan School of Public Health
- Joan B. Rose, Ph.D.
  Laboratory Director/Principal Investigator
  Homer Nowlin Chair in Water Research
  Co-Director Center for Water Sciences and
  Center for Advancing Microbial Risk Assessment
  Department of Fisheries and Wildlife
  Michigan State University
- Robert Sills
  MDEQ
  Toxicologist
- Joy Taylor Morgan
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- John Tilden
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- Dr. Eric Wildfang
  MDEQ
  Toxicologist
- Robert Delaney
  MDEQ
  Project Manager – WAFB

PFCs are on the short list of chemicals that might be at least partially responsible for the human health crisis. Their ubiquitous nature in the environment, in our homes, in our food, water, and human blood, along with their almost indestructible nature in the environment, make them a high priority in the research community and for governments around the world. The focus group should also research this family of contaminants specifically. The levels of contamination in the Great Lakes and biota in Michigan indicate a significant exposure to Michigan citizens and ecosystems.

The very widespread contamination of the former WAFB by PFCs can serve as an illustration of the challenges these contaminants will pose to regulators and parties trying to address these releases. More "WAFBs" will be found across the state. Communities with fire training facilities, other Department of Defense (DOD) bases, metal platers, other major airports, major transportation corridors, and other industrialized areas all could have extensive contamination by PFCs. Millions of dollars have been spent at WAFB addressing "conventional" contamination, such as chlorinated solvents, landfill leachate, and jet fuel. Yet for all the millions spent, the remedies are not sufficient to protect human health or the environment because of the PFC contamination. This could be the case at many other sites across the state. Given the levels of contamination recorded in the Great Lakes, other sites are likely as contaminated as WAFB is proving to be.

Cultural and Political Challenges

There are numerous things that state government could do to help fill data gaps on the epidemiological relevance of these problems to Michigan, advance the science of toxicology and epidemiology with regard to protecting our citizens and ecosystems, and developing policies and programs to effectively protect our children and their environment. However, in the current political, economic, and social environment, people are not willing to listen, regulate, fund and sacrifice to address the problem. There are many reasons for this and fixing that problem is beyond the scope of this write-up. However, it has to be recognized that no matter how well reasoned and fact based the conclusions of the focus group are, they will get little or no traction towards solutions without political buy-in by opinion leaders. For example, even though a second bridge to Canada makes complete economic sense, one man with a lot of money can thwart the actions of the Governor (but we have a Governor that does not give up easily).

Thus, going to the legislature and presenting the case at this juncture would be highly premature. I believe the Governor and Lieutenant Governor should be brought in when the Directors are satisfied that there is a real problem, and a comprehensive strategy on moving forward to protect the citizens, working with the legislature, should be developed.

In the interim, once upper management is convinced, the urgency of the problem should be communicated in any venue that the Directors and their lead staff are given the opportunity to influence. Also, academics that are thoroughly versed in the problems should be given platforms from which to speak as well. A unified message going out from multiple sources, so that "common knowledge" is

created amongst various advocacy groups (think of the advocacy groups for multiple sclerosis (MS), autism, attention deficit hyperactivity disorder, birth defects, breast cancer, etc.) would be an effective way of building the consensus in the public that the problem is real, and that we can do something about it. We do not have to just be victims.

Further Recommendations

Although solutions are not difficult to generate, the problem is creating what I call, "want to." If we "want to" do something as a society, organization, or individual, we are most of the way home to getting it done. We have plenty of smart people, we can muster all the resources we need and we have incredible technology for meeting challenges. The difficulty is to recognize the real challenges and make these items the priorities. That is why I have so emphasized that the Director be fully certain that there truly is a crisis to be dealt with. Once convinced, I am confident that the Director would get things done.

Still, I have already encountered plenty of doubt that anything could be done, so I want to give examples of things that could be done. So, here are some example recommendations (based mostly on PFC contamination which I am most familiar with) that the focus group might advocate.

- Funding additional dose response studies on PFOS, PFOA, and other PFCs that are found in the common contaminant mixtures and exploring the differences in toxicity of PFCs between humans and lower species. There are very few dose response studies on PFCs; however, risk based criteria development for drinking water, surface water, risk advisories, and direct contact all depend on these studies. The more studies that are completed, the greater certainty that criteria reflect true risks. Dose response studies are more tedious, do not break new scientific ground, and do not attract grant money and academic interest the way other toxicity studies do. Although these studies are not glamorous, they provide the fundamental science upon which regulation and risk management rely. The government can task academics and provide funding to perform these studies. The most accurate studies are done on large animals such as monkeys and pigs. These studies are the most time consuming and expensive; therefore, very few of them are completed.

  Lower species studies are sufficient most of the time; however, there appear to be major differences between lab animal and human toxic responses to PFCs (even between humans and monkeys). If we are facing a true human health crisis, then getting to the bottom of the question as quickly as possible, with as much certainty as possible, makes economic and social sense. Decision makers have to understand the academic bias (due to what drives funding success) against doing these very necessary studies. We simply have to know, for instance, if environmentally relevant doses of PFCs are causing these serious neurologic and autoimmune diseases. The studies may seem expensive, but their cost is miniscule compared to the cost of just dealing with a handful of children with lupus, MS, or autism.

  As there is increasing evidence that there seems to be a link between dysfunctional immune responses in the mother and the fetus (even with autism), pig studies (as their immune systems are similar to ours) might be very beneficial when it comes to exploring the link between environmental contaminants and immune system dysfunction (such as the autoimmune diseases). Again, it needs to be determined if the toxic effects on pigs are the same as for humans before even these studies could be relied upon with certainty.

- Order a thorough review of the results of the C8 study. These human studies already document that our exposures are too high.

- Sample blood serum, hair, and/or fingernails of people from across the state for PFC contamination (the same could be done for other suspect chemicals). Map the findings and figure out where our

biggest problems are. Begin to determine where the worst contamination is in the state. Try to isolate the causes of higher levels of contamination in the blood of the worst areas. Track changes in contaminant levels in human blood over time to monitor how policies, programs, regulations, voluntary efforts, and education are being effective at lowering people's exposures to dangerous chemicals.

- Umbilical cord blood should also be monitored across the state for contaminants. Are efforts to lower exposures to PCBs, dioxins and mercury having the desired effects over time? What new contaminants are increasing in the womb? What are the trends for unregulated contaminants?
- Check our food supply for contaminants. There are two things that have happened with regard to PFCs that will be effecting what is in the food we eat. For many applications, the producers of PFCs have replaced the long chain PFCs with short chain PFCs. Are these chemicals going up in our food supply and drinking water? Are they truly less toxic?

  The second thing that has occurred is that Brazil and China began to manufacture long chain PFCs after U.S. and European manufacturers ceased making them. Thus, PFCs have been going up in the blood of the Chinese, and probably the Brazilians' blood as well. What is happening with regard to the food that is coming into our country from these countries?
- Virtually no toxicity testing has been done on a host of PFCs and PFC telomers. If we find that these telomers and other PFCs are ubiquitous in the environment and blood serum, then the state, in conjunction with our universities, could fund and perform some basic toxicological testing on the more prevalent contaminants.
- The Director could contact high level Air Force Staff at the Secretariat level through the Environmental Council of the States, and discuss the need for collaboration on the investigations at the former WAFB. The state should truly try to avoid the "enforcement" based model of interacting with the Air Force on exploring the problems at the base. There is too much opportunity to work with the state universities, EPA, and MDEQ for the advancement of our understanding of PFC contamination, the risks they pose, the possible solutions, and the widespread implications of PFC contamination for the rest of the state, to not do the best we can to prevent biased or inadequate studies at the site. If the Air Force acts as if the state and everyone is out to get them, and works to shield themselves rather than letting the science go where it will, it would be an enormous opportunity lost. Truly, if the human health crisis is not real or PFCs have no connection to the problem, then just letting things take their normal course under existing law or whatever becomes of Part 201 makes total sense.

  However, on the chance that PFCs really are having a destructive effect on human health and the environment, then WAFB provides almost the perfect "laboratory" to study PFCs in the environment, biota, and humans for the following reasons.

  - There is no corporation that has to fear for its existence.
  - WAFB is littered with monitoring wells.
  - WAFB has an existing geographic information system.
  - WAFB has an existing groundwater model.
  - WAFB has been the site of many university and private enterprise research projects with extensive literature already published on the site.
  - Contamination in Clarks Marsh and fish are controlled by dams and so very unique populations of fish are exposed to specific levels of contamination.
  - Certain human subpopulations can be identified whose contaminant dose can be reconstructed and contaminants in their blood can be "finger printed" for different exposures around the base and in their general home environment.
  - The U.S. Forest Service has quality staff on site to assist in investigations and community outreach.

  - The Au Sable is an important resource to the state.
- Water testing of private wells and municipal wells could be done around the state for PFC analysis. A program of placing in-home charcoal filtering systems could be created. The U.S. decided to go from analogue to digital television and developed a system to help people make the transition. A similar approach could be taken to get as many people off impacted water as possible.
- A general statewide investigation of the levels of contamination in streams, lakes, sediment, and biota would help pin point areas of concern to be further investigated. Airports and military bases are obvious suspect point sources of PFCs. How bad are our transportation corridors and industrial areas contaminated? How much is storm water run off affecting our streams? Are other point sources major problems, such as local fire training facilities, historical industrial fire sites, car washes, municipal and industrial landfills, wastewater treatment plants, wastewater sludges, and the lands they have been applied to, metal platers, etc.?
- The state could direct and fund an effort to analyze consumer products for PFCs and other potential contaminants. The purpose of this would be to allow consumers to make choices on what they wanted to expose themselves and their children to. Certain types of products should be targeted for analysis such as personal grooming products and products that can easily disperse chemicals into the home and the environment, such as synthetic oils, washing fluids, textiles, etc. So many products have proprietary formulas or are contaminated with a chemical, and consumers have no way to make choices. The state, through the universities or MDCH, could provide the basic information for people that want to avoid certain chemicals.
- An annual conference (possibly hosted by Brian Calley) of health advocacy groups, academia, social welfare, and environmental advocacy groups could be organized to discuss the impacts of environmental contaminants on human health and the environment (driven by research from the academic community).
- Michigan should become a member state in the Center for Disease Control's Autism and Developmental Disabilities Network. The methods used to track these disorders are rigorous and would produce excellent data on trends in these diseases in Michigan.

The Complicating Factor

Major corporations have an enormous economic stake in the outcome of the toxicological and epidemiological studies of PFCs. The leadership of the state, if they are to be effective, must understand that these pressures will likely lead to "scientific" studies that tend to cloud the issues. One only has to remember what happened with the campaign to eliminate smoking and the amount of confusion created by "studies" that showed smoking was safe. These studies, although appearing to the public and policy makers to be legitimate scientific enquiry were nonetheless spurious. They were completed in order to prevent government action and lawsuits. There is evidence that some industrial entities may try the same thing with PFCs. I would direct the reader to the attached letter, dated April 29, 2003, prepared by P. Terrence Gaffney. Esq. of the Weinberg Group, Inc., to Jane Brooks, Vice President, DuPont de Nemours & Company (DuPont) concerning PFOA contamination, where Mr. Gaffney outlines a strategy to "shape the debate at all levels" and, "discourages governmental agencies….from pursuing this matter any further" (Thacker, 2006). This is not an accusation towards DuPont, but there are many more corporations that have a large stake in this as well. These enormous stakes for many corporations are created not only because of the potential for real harm, but also due to the fact that we are in a litigious and fault finding culture. One cannot expect every corporation to rise above their own interests in order to protect the public and the environment. Disinformation, spurious studies, political power games, slander, and a host of other tactics will likely be used in an

attempt to prevent the public and policy makers from understanding the true risks posed by these contaminants.

When the Director gets an independent assessment of this write up, he should be aware that several professors from Michigan schools are under contract from 3M. They should disclose such a connection if contacted, but prior vetting would be a more certain way to assure objectivity.

Conclusion

There is an endless list of things that could and possibly should be done. However, first, those in authority have to be convinced that there is a crisis.

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July 5, 2012

Attachment

References

P.D.Thacker, “The Weinberg Proposal” Environmental Science & Technology,” *Environ. Sci. Technol.,* Vol. 40, No. 9, 2006, pp. 2868-2869. http://pubs.acs.org/doi/abs/10.1021/es0630137

Photograph by Lance Booth, *Daily Herald*

July 2012

U.S.—July means frolicking with goggles in a spray of firefighting foam in Lehi, Utah. The tradition, now in its fourth year, takes place this month to celebrate Pioneer Day, a state holiday honoring the 1847 arrival of Mormons in the Salt Lake Valley.

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THE WEINBERG GROUP INC.

April 29, 2003

Jane Brooks
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Re: Perfluorooctanoic acid (PFOA)

Dear Ms. Brooks:

I am preparing this letter in anticipation of our meeting on April 29, 2003 in Washington, DC. This piece is intended to describe the services THE WEINBERG GROUP INC. can provide regarding issues related to perfluorochemicals generally and perfluorooctanoic acid (PFOA) in particular. Please note that this has been prepared prior to our initial meeting. I will most certainly follow up after our meeting with more specific ideas and recommendations after we have had the opportunity to discuss DuPont's concerns in greater detail.

The constant theme which permeates our recommendations on the issues faced by DuPont is that **DUPONT MUST SHAPE THE DEBATE AT ALL LEVELS.** We must implement a strategy at the outset which discourages governmental agencies, the plaintiff's bar, and misguided environmental groups from pursuing this matter any further than the current risk assessment contemplated by the Environmental Protection Agency (EPA) and the matter pending in West Virginia. We strive to end this now.

For 23 years. THE WEINBERG GROUP has helped numerous companies manage issues allegedly related to environmental exposures. Beginning with Agent Orange in 1983, we have successfully guided clients through myriad regulatory, litigation, and public relations challenges posed by those whose agenda is to grossly over regulate, extract settlements from, or otherwise damage the chemical manufacturing industry.

As we understand the situation, there is currently a great deal of attention focused on the safety of perfluorochemicals generally and PFOA in particular. Specifically, due to the situation in West Virginia and the activities of Environmental Working Group, the threat of expanded

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litigation and additional regulation by the EPA has become acute. In response to this threat, it is necessary for DuPont to prepare an overall technical and scientific defense strategy. We can assist with all phases of the technical and scientific defense, but more importantly, shape the debate and direction of the PFOA issue. The recent ruling by Judge Hill regarding blood testing underscores the need to act quickly and forcefully. The following will describe some of our capabilities in assessing the scientific facts, developing appropriate responses or sound scientific messages, building a team of world class experts to deliver those messages, and implementing a strategy to limit the effect of litigation and regulation on the revenue stream generated by PFOA.

DEVELOPMENT OF BROAD TECHNICAL DEFENSE STRATEGY

For over two decades, clients have repeatedly communicated to us that of all the services we provide, the most valued is our ability to provide an overall science-based defense strategy. This strategy can be applied to litigation, regulatory, or legislative problems that cause a particular product to be under pressure. Specifically, during the initial phase of our engagement by a client, we will harness, focus, and involve the scientific and intellectual capital of our company with one goal in mind—creating the outcome our client desires. This will entail the coordinated and focused compilation of specialists within THE WEINBERG GROUP to receive, review, and analyze all available relevant data regarding PFOA in particular, and polyfluorochemicals in general. These in-house experts are scientists and physicians holding advanced degrees in such areas as epidemiology & biostatistics, pharmacology, pathology, toxicology, oncology, molecular biology, regulatory strategy, and product defense.

The outcome of this process will result in the preparation of a multifaceted plan to take control of the ongoing risk assessment by the EPA, looming regulatory challenges, likely litigation, and almost certain medical monitoring hurdles. The primary focus of this endeavor is to strive to create the climate and conditions that will obviate, or at the very least, minimize ongoing litigation and contemplated regulation relating to PFOA. This would include facilitating the publication of papers and articles dispelling the alleged nexus between PFOA and teratogenicity as well as other claimed harm. We would also lay the foundation for creating Daubert precedent to discourage additional lawsuits.
THE WEINBERG GROUP would also prepare an all-encompassing strategy to meet public relations issues and, if necessary, prepare company representatives for testifying before governmental bodies. These are but a few of the services we provide.

It is also important to note that these services will not be duplicative of the services provided by law firms and public relations firms. Although we work closely with counsel and other consultants, our services are distinct and science-based.

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Over the past thirty years, the perfluorochemical industry has amassed a plethora of scientific data on the safety of PFOA. Many in the industry are convinced, with good reason, that PFOA is safe. They would cite numerous studies and conclusions reached by a broad spectrum of scientists. All of this is good, and certainly well intended, but the current litigation and regulatory climate demands a fresh new approach. In our opinion, it matters little that the industry is satisfied PFOA is safe. The real issue is the perception *outside* the industry. This battle must be won in the minds of the regulators, judges, potential jurors, and the plaintiff's bar. The recent certification by numerous federal courts of medical monitoring classes as well as the organization, sophistication, and financial strength of the plaintiff's bar require an aggressive, relentless strategy be implemented and driven by the manufacturers. Manufacturers must be the aggressors. A defensive posture, in our opinion, would be disastrous. THE WEINBERG GROUP can help DuPont take the lead on issues related to PFOA. We would suggest a multifaceted approach be implemented immediately.

WHAT WE DO

As the leading scientific consulting firm in the world, THE WEINBERG GROUP serves industries in four areas, the first of which is development, registration and support of pharmaceuticals, biologics, and devices. Other services deal with environmental, health and safety issues through the use of the latest information and techniques establishing risk levels and risk management techniques and organization of technical functions such as quality assurance and toxicological, clinical and epidemiological studies. In the fourth area, we provide science-based advocacy to help deal with emerging business problems in litigation, legislation and regulation. Our staff has a broad base of experience supporting counsel and their clients in responding to demands for damages, punitive rewards, reimbursement and future medical monitoring costs for personal injury and fraud associated with drugs, corporate conduct, and failure to provide the correct information to the public or legislators and regulators. Specifically, in the area of Science-Based Advocacy, we assist with:

- analysis of plaintiffs' best case and defendants' best response as a tool for strategy and tactical development;
- expert witness, spokesperson and panel identification and development in all issues in litigation;
- preparation of counsel for discovery, deposition, negotiation, and trial;
- records review, analysis, and organization;
- preparation of primers describing critical issues and including approaches such as affidavits for use in summary judgment and opposition to class certification;
- document retrieval, management and analysis;
- unique development of experts with chemical, medical, epidemiological, biologics, regulatory, and legislative backgrounds;
- a variety of public relations programs needed to create jury understanding of the issues; and

- Creation of exhibits, audiovisual presentations, and other devices to enhance lay understanding of the issues in dispute, most notably the complex scientific concepts to be digested in defense arguments.

Ours is a task-oriented organization in which clients make specific assignments under carefully planned, client-controlled budgets. Our experience in environmental exposure matters has repeatedly illustrated our client's need to control as many variables of liability exposure as possible. In addition, some preliminary suggestions of tasks for managing issue related to PFOA include:

- develop "blue ribbon panels" of thought leaders on issues related to PFOA **IN REGIONS WHERE MANUFACTURING PLANTS ARE LOCATED** to create awareness of safety regarding PFOA in areas of likely litigation, and in particular where medical monitoring claims may be brought;
- develop an aggressive campaign focused on the safety and utility of PFOA and the products it in which it is used;
- coordinate the retrieval, organization, and analysis of literature to date (both internal and external) regarding safety of PFOA and create a centralized searchable database for industry use;
- begin to identify and retain leading scientists to consult on the range of issues involving PFOA so as to develop a premium expert panel and concurrently conflict out experts from consulting with plaintiffs;
- begin to coordinate focus groups of mock jurors to determine the best "themes" for defense verdicts and perspectives on management of company documents and company conduct;
- reshape the debate by identifying the likely known health benefits of PFOA exposure by analyzing existing data, and/or constructing a study to establish not only that PFOA is safe over a range of serum concentration levels, but that it offers real health benefits (oxygen carrying capacity and prevention of CAD);
- coordinate the publishing of white papers on PFOA, junk science and the limits of medical monitoring;
- work with industry lobbyists to ensure they remain on message regarding the scientific issues related to PFOA;
- provide the strategy to illustrate how epidemiological association has little or nothing to do with individual causation, and:
- begin to shape the Daubert standards in ways most beneficial to manufactures.

THE WEINBERG GROUP has developed an understanding of the variety of approaches needed to deal with each of these issues. Indeed, we have trial experience in these issues as well.

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I want to reiterate that we already have extensive experience in helping a Fortune 40 client with a very similar compound to PFOA. Our experience and knowledge regarding this compound is very well established. We do not need to educate ourselves at DuPont's expense.

I again stress that this was prepared prior to our initial meeting, but I wanted to provide material for you to ruminate upon before our next discussion on these issues. Thank you again for the opportunity to be of service.

Sincerely,

P. Terrence Gaffney, Esq.
Vice President
Product Defense
THE WEINBERG GROUP INC.

PTG/lhp

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